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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GASTROENTEROLOGY AND UROLOGY DEVICES PANEL

+ + +

May 17, 2017
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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M E E T I N G

(8:04 a.m.)

DR. SCHWAITZBERG: Good morning. I'd like to call the meeting of the Gastroenterology and Urology Devices Panel to order.

My name is Dr. Steven Schwaitzberg. I'm the Chairperson of this Panel. I am the chairman of the Department of Surgery for the University at Buffalo. Previously, I worked at Harvard Medical School, and before that, Tufts University.

I'd like to take this opportunity for the Panel to introduce themselves. We'll start on this side. If you could introduce what your role is and where you're from.

MS. BARNES: Hi, my name is Teresa Barnes. I am a patient advocate, and I just recently moved to St. Louis.

MR. FRANKEL: Hi. Naftali Frankel, Consumer Rep.

MR. THURAMALLA: Good morning. Naveen Thuramalla. I am the Industry Rep. I am the Vice President of Regulatory Affairs at ARKRAY.

DR. CONNOR: Jason Connor, Berry Consultants, clinical trialist and statistician and an assistant professor at the University of Central Florida College of Medicine.

DR. O'CONNOR: I'm Michael O'Connor. I'm from the University of Chicago. I'm an anesthesiologist and intensivist.

MR. STAMMERS: Al Stammers. I'm Director of Research and Quality at SpecialtyCare in Nashville, Tennessee.

DR. KRUPNICK: Sasha Krupnick, thoracic surgery, University of Virginia.

DR. VAN BERKEL: I'm Victor van Berkel. I am a thoracic surgeon at the University of Louisville.

DR. HAMMON: I'm John Hammon. I am a cardiothoracic surgeon from Wake Forest University in Winston-Salem, North Carolina.

DR. AFIFI: I'm Abdelmonem Afifi, Professor of Biostatistics at the Fielding School of Public Health at UCLA.

DR. YUH: Good morning. I'm David Yuh. I'm the Chair of Surgery at Stamford Hospital in Stamford, Connecticut, and I am a cardiothoracic surgeon.

MR. RILEY: Good morning. Jeff Riley. I am a perfusionist at the University Hospitals Cleveland Medical Center.

DR. YUSEN: Good morning. Roger Yusen. I am a pulmonary and critical care physician, lung transplant pulmonologist at Washington University in St. Louis.

DR. NATHAN: Steve Nathan, transplant pulmonologist at Inova Fairfax Hospital, Falls Church, Virginia.

DR. MEYER: Dan Meyer, cardiothoracic surgery, Methodist Health System in Dallas and previously involved with the thoracic committee with UNOS.

DR. MOON: Marc Moon. I am a cardiac surgeon at Washington University in St. Louis.

DR. FISHER: Good morning. I'm Ben Fisher, the Director of the Division of Reproductive, Gastro-Renal, and Urological Devices, fondly known as DR. GUD, for the Center for Devices and Radiological Health.

DR. SCHWAITZBERG: I'd like to note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that all Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval for the TransMedics Organ Care System (OCS) Lung System.

Before we begin, I'd ask our distinguished Panel members and the FDA staff seated,

which we've already done, to introduce yourselves.

If you have not already done so, please sign the attendance sheets.

To my left is Ms. Aden Asefa, the Designated Federal Officer for the Gastroenterology and Urology Devices Panel. She will make some introductory remarks.

MS. ASEFA: Good morning. I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary

employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application for the TransMedics Organ Care System (OCS) Lung System, sponsored by TransMedics, Incorporated. The TransMedics Organ Care System Lung System is a portable organ perfusion, ventilation, and monitoring medical device intended to preserve donor lungs in a near physiological, ventilated, and perfused state for transplantation.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section (b)(3) to Dr. Steven Nathan. Dr. Nathan's waiver addresses his personal investments in stock funds that contain underlying asset shares of a firm that makes a product which would compete with the Sponsor's device. The total magnitude of the funds is between $100,001 and $200,000.

The waiver allows individuals to participate fully in the Panel deliberations. FDA's reasons for issuing this waiver are described in the waiver documents which are posted in FDA's website at www.fda.gov. Copies of the waiver may also be obtained by submitting a written request to the Agency's Division of Freedom of Information.

Mr. Naveen Thuramalla is serving as the Industry Representative, acting on behalf of all related industry, and is employed by ARKRAY, Incorporated.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

I will now read the Temporary Voting Memorandum.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Gastroenterology and Urology Devices Panel for the duration of the meeting on May 17th, 2017:

Jason Connor, John Hammon, Alexander Sasha Krupnick, Dan Meyer, Steven D. Nathan, Michael O'Connor, Jeffrey B. Riley, Alfred H. Stammers, Victor H. van Berkel, David D. Yuh, Roger Yusen.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This has been signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on April 18th, 2017.

For the duration of the Gastroenterology and Urology Devices Panel meeting on May 17th, 2017, Teresa Barnes Tosi has been appointed to serve as a Temporary Non-Voting Member, and Dr. Marc Moon has been appointed to serve as a Temporary Voting Member. For the record, Ms. Barnes, the Patient Representative, serves as a consultant to the Pulmonary Allergy Drugs Advisory Committee at the Center for Drug Evaluation and Research, and Dr. Moon serves as a consultant to the Pediatric Advisory Committee in the Office of Pediatric Therapeutics. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

The appointment was authorized by Dr. Janice Soreth, Associate Commissioner for Special Medical Programs, on May 3rd, 2017.

Before I turn the meeting back over to Dr. Schwaitzberg, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table outside of the meeting room.

The press contact for today's meeting is Ms. Theresa Eisenman.

I would like to remind everyone that the members of the public and press are not to be permitted in the Panel area, which is the area beyond the speaker's podium. I request that the reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. Artair Mallett at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

And, finally, please silence your cell phones and other electronic devices at this time. Thank you very much.

And Dr. Schwaitzberg.

DR. SCHWAITZBERG: Thank you, Aden.

We'll now proceed to the Sponsor's presentation. I would like to invite the Sponsor to approach the podium.

I will remind the public observers at this meeting, while this is open for public

observation, attendees may not participate without the request of the Panel Chair.

I would also ask the Sponsor and all presenters to avoid excessive jargon, excessive use of abbreviations, so that an accurate transcript and clear understanding of what you're trying to say is made available to everybody who may not be as familiar with the terms that you've been living with.

The Sponsor will have 90 minutes. We are 1 minute behind schedule, so we will end in 45 minutes. Sorry, 90 minutes. You may proceed.

(Laughter.)

DR. SCHWAITZBERG: They told me to speed this up.

DR. HASSANEIN: Can I get the microphone, please? Thank you.

Good morning. My name is Waleed Hassanein. I am the President and Chief Executive Officer of TransMedics. Before TransMedics, I was a cardiothoracic research fellow at the Brigham and Women's Hospital and West Roxbury VA in Boston. And prior to that, I was a general surgery resident here at Georgetown University Medical Center, where I graduated from medical school.

Thank you, Mr. Chairman and Dr. Fisher, for the opportunity to present the OCS Lung INSPIRE trial supporting the safety and effectiveness of the Organ Care System for lung preservation for transplant. I would like to start my presentation by acknowledging that there are areas of clinical disagreement with FDA on certain aspects of the trial design and results. We respect FDA's views. One of our intentions today is to provide clarification on these issues based on facts and published clinical literature.

I would like to remind the respected panelists that we are going to emphasize that the INSPIRE trial was the first-of-its-kind international randomized trial in the field of organ preservation for transplant. We had to overcome several complexities of organ retrieval and allocation process. There have been valuable learnings from the INSPIRE trial for

TransMedics and for our investigators. However, we are proud of the fact that we successfully completed this large trial of 349 patients in 21 international academic lung transplant centers in 9 different countries in 3 different continents.

Most importantly, the goal of our presentation today is to share with the Committee the results of the largest body of clinical evidence supporting the use of ex vivo lung perfusion technology for lung transplantation.

Finally, we are deeply humbled that after 2 decades of research and development, here we stand at this critical milestone that could potentially enable this lifesaving technology to be available to U.S. patients for lung transplant.

TransMedics is a clinically driven organization. The origin of the Organ Care System technology started and began as an academic cardiothoracic research project in Boston. This project started in '95 and ended in '98, and in 1998 this project was recognized as one of the national finalists for the American Association of Thoracic Surgeons Research Award in 1998. In 2000 TransMedics began the formal development of the Organ Care System technology to maintain human organs in near physiologic and functioning state, to overcome limitations of cold storage that Dr. Gabriel Loor will discuss later.

Over nearly 2 decades, TransMedics has developed the Organ Care System platform for three organs: lung, heart, and liver preservation for transplant. All three organs are approved outside of the U.S., and to date, we have more than 800 transplanted human patients, worldwide, performed on the OCS heart, lung, and liver platform.

TransMedics has sponsored the largest number and the largest size clinical trials of any preservation technology worldwide. We did this because we are committed to the highest level of establishing clinical evidence for the OCS platform for all types of organs.

TransMedics collaborates with global academic leaders of organ transplantation to oversee and conduct these complex trials, and many of whom are here today.

Our focus today, obviously, is on the INSPIRE lung trial and standard criteria donor lungs for transplant.

TransMedics developed the Organ Care System to address limitations of cold storage; namely, the OCS was designed to reduce ischemic injury in the donor lung through the use of warm oxygenated blood perfusion. The OCS also allows transplant clinicians to monitor and optimize the lung condition while the lung is being preserved. For example, we are constantly ventilating the lung. We can perform maneuvers to open up segments of the donor lung that may not be adequately ventilated.

Furthermore, the OCS enables ex vivo metabolic and functional assessment of the organ. For the lung, we can assess oxygenation capacity using standard blood gases, vascular resistance, airway pressures as well as bronchoscopy, as shown here in this photo.

OCS Lung is an integrated, portable, ex vivo perfusion and ventilation system for donor lung preservation. It comprises three components: the OCS lung console, the OCS lung perfusion module where the lung and the perfusate resides, and the OCS solution, shown here.

Let me show you a short video to demonstrate how the OCS works from the lung leaving the donor until the lung reaches the recipient.

(Video played.)

DR. HASSANEIN: This is the lung in OCS ventilated and perfused. The lung comes out of the donor after standard flush. The lung is cannulated with two cannulas, one cannula that will go into the trachea for ventilation, seen here, and another cannula to the pulmonary artery for perfusion. The OCS is set following a checklist in an iPad application. And then the lung is now connected to the active ventilation and perfusion circuit using the same two connections that were established earlier. And you can see here, the pulmonary artery is being de-aired, and the lung is ready to start perfusion.

The temperature is raised gradually up until it reaches 37 degrees, and at around 37 degrees, the ventilation process starts. Once the lung begins ventilation, the lung is wrapped in a biocompatible film to secure the lung to the organ chamber but also to prevent over-inflation and prevent barotrauma during transport.

If an assessment is required either at the donor or recipient site, there's a built-in bronchoscopy port where the transplant physician or pulmonologist or surgeon can assess the bronchoalveolar tree or the physiologic parameters, perfusion pressures, airway pressures; both live and trend are displayed on a wireless monitor, but also they're stored at a 2-minute average in an SD card that's built into the device. Now the lung is ventilated and perfused, and now the lung is ready to be transported from the donor hospital to the recipient hospital.

(Video ended.)

DR. HASSANEIN: Let me summarize this section by saying the INSPIRE is the largest prospective body of clinical evidence supporting portable ex vivo perfusion and preservation for lung transplant. The results that will be presented here today, and the totality of the clinical evidence from the INSPIRE trial provides ample assurance of safety and effectiveness for the OCS Lung System.

The OCS Lung System met its primary effectiveness and safety endpoint. There was significant reduction, clinically significant reduction, of incidence of primary graft dysfunction Grade 3 within the first 72 hours after lung transplant. This is the first technology to show a decrease in PGD3, which is a serious complication following lung transplantation. Importantly, the safety profile of the OCS Lung System was similar to the standard of care, cold storage. Finally, there were several clinical benefits that will be further studied in our proposed post-approval plan.

If we earn your support for approval, the indication for use statement will be as

follows: The TransMedics Organ Care System Lung is a portable organ perfusion, ventilation, and monitoring medical device to preserve donor lungs in a near physiologic, ventilated, and perfused state for transplantation.

The agenda for the rest of the presentation will go as follows: Dr. Gabriel Loor from Baylor St. Luke's Medical Center will discuss the limitation of cold storage and clinical needs in lung transplant. I will discuss the regulatory history of the OCS Lung System and the INSPIRE trial. Dr. Ardehali from UCLA and one of the co-principal investigators of the INSPIRE trial will discuss the trial design. Professor John Wallwork from Cambridge, England, the INSPIRE trial medical monitor, will describe the trial adjudication process. Dr. Gregor Warnecke, Chief of Lung Transplantation in Hannover Medical School and the other co-principal investigator of the INSPIRE trial, will review the trial clinical results. I will return to review the TransMedics training program and post-approval studies. And then, finally, Professor Dirk Van Raemdonck, the chief of the transplant center at University Hospitals in Leuven in Belgium and the co-chair of the ISHLT PGD working group, will conclude our presentation with the benefit-risk assessment.

We also have several additional experts who are here to answer any questions that the Committee may have.

Thank you for your attention. I would like to invite Dr. Gabriel Loor to discuss the clinical need and limitation of cold storage for lung preservation.

DR. LOOR: Good morning. My name is Gabriel Loor. I'm Associate Professor and Surgical Director of the Lung Transplant Program at the Michael E. DeBakey Department of Surgery at Baylor College of Medicine and Texas Heart Institute. I was the principal investigator for the University of Minnesota Medical Center in the INSPIRE lung trial.

I have no financial or equity interest in TransMedics and have not received compensation other than travel reimbursement to present here today.

After years of researching and helping end-stage lung disease patients, I'm pleased to discuss some of the important limitations we face today in the field of lung transplantation.

Transplantation is the gold standard for treating end-stage lung failure. Without a transplant, fewer than 50% of these patients will be alive in 1 to 2 years. For many who undergo the procedure, it can provide longer life expectancy, improve a person's functional status, and deliver a better quality of life.

Despite its success, there are several challenges facing lung transplantation today.

- Organ availability
- Older and sicker patients being prioritized on the wait list
- Preservation limitations and transplant logistics
- Primary graft dysfunction
- Bronchiolitis obliterans syndrome, or BOS, a form of chronic rejection affecting up to 50% of patients by 5 years

Over the last 3 decades, there have been many advancements in the field of lung transplantation: surgical techniques, pre- and perioperative care of transplant recipients, and changes in immunosuppression. In contrast, there have been no advancements made in organ preservation beyond cold storage.

Cold storage is bound by three key limitations: Donor lungs are subjected to time-dependent injury caused by ischemia reperfusion of the lungs. We have no ability to optimize the donor lung during its transport. Finally, we have no way to assess the viability of the lungs once they are taken from the donor and prior to transplant.

Cold ischemic time is the period of time when blood flow to the donor lung stops until it is reestablished in the recipient. This time is generally regarded as a negative factor in lung transplantation. Significant efforts are made to minimize this period. This

composite ISHLT report clearly demonstrates that in North America, most lung transplants are performed with less than 6 hours of total ischemic time, in an effort to reduce ischemia reperfusion injury on the lung graft.

A technology that can reduce ischemia during preservation would alleviate these clinical concerns and potentially expand our reach for transplantation.

Primary graft dysfunction, or PGD, is a form of acute lung injury that occurs when blood flow is reintroduced to the organ. It occurs within the first 72 hours after lung transplant, and it is routinely assessed at Time 0, 24 hours, 48 hours, and 72 hours.

The short-term morbidity associated with PGD at any time point includes severe hypoxemia, lung edema, and difficulty with ventilation. Based on clinical criteria, the ISHLT consensus guidelines categorizes PGD as absent or mild, which is Grade 0 or 1; moderate, which is Grade 2; or severe, which is Grade 3.

It's important to note that a critical period of ischemia is required for reperfusion injury or PGD to occur. Any technology that reduces ischemia would thus be valuable in the lung transplant community.

The incidence of severe PGD, or PGD3, is high within the initial 72 hours after transplant, even with our current practice of limiting ischemia to less than 6 hours. In a large 1,255-patient cohort in the lung transplant outcomes group, the incidence of PGD3 was 30.8% when assessed within the initial 72 hours after lung transplantation.

A growing body of scientific literature supports that early PGD3 is associated with poor long-term clinical outcomes. Whitson et al. demonstrated that patients with PGD Grade 3 at any time point between Time 0 and Time 48 hours had substantially lower long-term survival. In addition, Grade 3 PGD at these early time points increased the probability of developing bronchiolitis obliterans syndrome (BOS), a form of chronic allograft rejection.

Thus, PGD3 at any time point within 72 hours is important. Given the lack of available therapies to reduce this, we've become content with the notion that transient PGD3 is okay and that it will resolve. But any PGD3 matters.

Even PGD in the immediate post-transplant period is clinically significant. A study of 334 adult lung transplant recipients at Washington University in St. Louis reported that patients who experienced PGD3 at Time 0 after lung transplantation and survived past 90 days had a higher risk of developing BOS over a 6-year follow-up. The authors concluded that development of PGD3 in the immediate post-transplant period, or Time 0, is a significant independent risk factor for BOS and that there is a direct relationship between the severity of PGD and the risk of BOS.

A recent paper from UCLA demonstrated that even transient PGD, which was defined as PGD 2 or 3 at Time 0, which improved by 72 hours, was associated with twice the risk of developing BOS long term, compared to a patient that did not have PGD at Time 0. This data demonstrates that reducing the incidence of PGD3 at any time post-transplant would be expected to significantly improve patients' long-term outcomes, including PGD at Time 0.

Data from the last several slides will be useful as you consider the FDA's discussion questions this afternoon regarding the clinical relevance of PGD3 within 72 hours and particularly at Time 0.

Results from several studies, including the three that I have just highlighted, demonstrate that any PGD3 within 72 hours matters.

In summary, lung transplantation is the gold standard for the treatment of end-stage lung disease. But cold storage is unable to address several issues in standard lung transplantation, including ischemic injury and PGD3.

Data demonstrate that PGD3 at any time point within 72 hours is associated with

poor patient outcomes.

A technology that could minimize ischemic injury and allow for optimization and assessment during transport would be a welcome advance in the field of lung transplantation.

Thank you for your time. Dr. Hassanein will now review the regulatory history of the OCS lung INSPIRE trial.

DR. HASSANEIN: Thank you, Dr. Loor.

Please allow me to spend the next section of the presentation reviewing the regulatory history of the INSPIRE trial, to provide our perspective on several of the FDA discussion questions.

As the first randomized controlled trial in lung preservation, there were several challenges in the designing phase of the protocol of that trial. This includes determining the appropriate effectiveness endpoint, the appropriate analysis populations, the timing of the endpoint assessment. Furthermore, we had to find the most practical way to fit a randomization process in the complex lung allocation and retrieval workflow or process. As such, the FDA review process was complex and prolonged. Let me walk you through a timeline of the key regulatory decisions.

TransMedics submitted the IDE for INSPIRE trial, original IDE, in November 2010. The primary endpoint was 30-day patient survival. To capture the impact of preservation injury at an early time point post-transplant, we included the assessment of primary graft dysfunction Grade 3 in the early post-transplant phase at T24 as a secondary endpoint. The primary analysis population was per protocol, and the non-inferiority margin was proposed at 10%. FDA disagreed with key components of the proposed design.

We then spent nearly 2 years in study design negotiations with FDA. During this time, TransMedics sought the help of leading academic lung transplant experts and senior

regulatory advisors to help address these issues and find a way to get the trial started. Our position was supported by published literature similar to the ones shared with you by Dr. Loor as well as device trial design precedent. FDA required certain conditions for approval of this IDE that were very different from the original trial design. TransMedics ultimately agreed to these conditions in order to initiate the trial in the U.S. and avoid further delays.

FDA required a composite primary endpoint of 30-day patient survival and freedom from primary graft dysfunction Grade 3, but at the last time point, at T72. Furthermore, the primary analysis population had to be modified to modified ITT. And more importantly, a non-inferiority margin of no more than 4% was mandated.

TransMedics filed a protocol amendment in 2013 to realign the trial with the original clinical intent of the trial design. The composite primary endpoint was changed to 30-day survival, patient survival, and freedom from PGD3 within the entire window of 72 hours after lung transplant. Per protocol was redesignated as the primary analysis population for effectiveness.

As you have seen in the Panel Executive Summary, the FDA has taken the position that the protocol amendment was driven by interim data analysis of the INSPIRE trial. We acknowledged the INSPIRE trial from Day 1, from its inception, was an open-label study. I would like to make it very clear to the respected members of this Panel that before the first patient was enrolled in this study, our position has always been, as seen in this timeline, that PGD at an earlier time point is the more appropriate clinical endpoint of effectiveness for a preservation technology designed to minimize ischemic injury on the donor lung.

The revision of the primary endpoint was driven by published clinical evidence on the correlation between early PGD3 and poor long-term outcomes, many of which have been presented by Dr. Loor.

The timing of the actual amendment was driven primarily by a parallel IDE that we were negotiating with the same division with the FDA on the same exact topic of assessing PGD3 within 72 hours versus at 72 hours. And we finally had to appeal to the Director of the Office of Device Evaluation to independently adjudicate the scientific merits of assessing PGD3 within 72 hours in that other IDE.

The FDA ODE Director agreed with TransMedics' position that PGD3 within 72 hours was a clinically appropriate endpoint for the OCS lung. After that, we immediately filed the amendment to harmonize our endpoints between the original design that we proposed for INSPIRE and the other IDE, for consistency.

Given this background, now please let me address three key topics. The first topic is the non-inferiority design and margin used in the INSPIRE trial; the second is the rationale for the protocol amendment; and the third is the rationale for the administrative extension.

I will start with the non-inferiority design and the non-inferiority margin. INSPIRE was designed as a non-inferiority trial for several reasons: First, a non-inferiority design is very common for pivotal device trials in the U.S.; second, a non-inferiority design ensures that OCS would have to maintain the current success rate, short-term success rate, for lung transplantation today.

However, one of the most important considerations in the design of a non-inferiority trial design is the designation or the size of the non-inferiority margin. This graph displays the non-inferiority margins of five device trials in heart, lung, and liver failures and transplantation. As you can see, the non-inferiority margins ranged from 7.5% to 15%.

Based on this precedent, TransMedics proposed a non-inferiority margin initially at 10, and then we reduced it down to 7.5%. FDA mandated a margin of no more than 4% as a condition for approval for the INSPIRE trial. It's very important to consider what does a 4% non-inferiority margin mean and the practical implementation of that, of this extremely

narrow margin. To our knowledge, this is the narrowest margin that has ever been used for a pivotal therapeutic device trial. This sets an extraordinarily high bar for success.

Second, with the sample size we enrolled, the OCS arm had to perform at least 4 to 5 percentage points better than the control in order to achieve significance in the non-inferiority test.

Next, I will discuss the rationale for our protocol amendment. The protocol amendment was filed to address two points. First, the endpoint was modified to only analyze primary graft dysfunction Grade 3 comprehensively within the 72 hours post-transplant instead of a single time point, which is at T72. Second, we redesignated the per-protocol population as the primary analysis population of effectiveness. Please let me share the clinical rationale for these two changes.

The first element of approved protocol amendment was an analysis of PGD3 within 72 hours as an appropriate clinical endpoint based on the following:

One, PGD3 within 72 hours comprehensively assesses the incidence of severe graft dysfunction in the post-transplant period. As you've seen in Dr. Loor's review of the literature, the literature supports PGD3 at early time points as predictive of poor long-term outcomes after lung transplant.

Second, TransMedics consistently maintained the assessment of PGD3 at early time point was the most relevant measure for a preservation technology designed to minimize ischemic injury on the donor lung. PGD3 within 72 hours captures all these time points, including T0, T24, T48, up to T72.

One important point to note, and this is important in your deliberation later this afternoon, from Day 1, the INSPIRE trial protocol collected PGD at every time point after transplantation: T0, T24, T48, and T72. Therefore, analyzing PGD at all four time points as a part of the protocol amendment did not change the type of data being collected, the

manner of its being collected, or the timing of its collection.

Let me discuss the second element of the amendment, which was redesignation of the per-protocol as the primary analysis population.

TransMedics maintained throughout the review process that the per-protocol population was the most appropriate primary analysis based on two main factors:

- First, the FDA's own guidance document that supports the per-protocol analysis as a preferred analysis for some non-inferiority trials;
- Second, in this trial, the per-protocol population assesses the treatment effect of the preservation technology, which is OCS Lung System, versus cold ischemic storage when both treatments are used as intended.

Please allow me to provide a few practical clinical examples why per-protocol provides a more accurate clinical assessment of the performance of the OCS system.

First is a scenario where a patient is randomized to OCS but transplanted with a lung that was preserved using cold storage. In the per-protocol population, this patient would be excluded from the OCS results. However, in the mITT population as defined in our protocol, the results of this patient would be included in the OCS arm and will be analyzed and reported in the OCS arm, though the transplant occurred with a lung that was preserved using standard cold ischemic storage.

One other example that supports the use of per protocol: When a patient is transplanted with a donor lung that did not meet eligibility criteria that was pre-specified for the trial (for example, active pneumonia, severe COPD), again, in the per-protocol population, this patient will be excluded from the OCS arm analysis. However, in the mITT, the results of this patient will be included in the OCS arm even though they were transplanted with a lung that was not eligible for the study.

For comprehensiveness and rigor, we will present the results for both the primary

analysis population (per protocol) as well as a sensitivity analysis, which is the modified ITT.

The last topic I would like to review is the administrative extension cohort and a related issue, the use of two different preservation solutions with the OCS Lung System in the INSPIRE trial.

The IDE was approved to allow two solutions to perfuse donor lungs on the OCS. One is the OCS lung solution and another commercially available solution called low potassium dextran solution. We intended that the primary solution to be used is the OCS lung solution, given this is the solution that we manufacture and this is the solution that we are requesting your review of today. However, due to an unanticipated supply shortage situation, investigators used LPD solution for a few months during the trial.

During this period, investigators reported to TransMedics that the observed lungs that were preserved using the LPD solution had edema coming out of the OCS system. We promptly notified FDA to seek their advice about the potential next steps.

An administrative extension was approved for enrolling additional subjects to keep the trial sites open while we define a mutually acceptable plan. Ultimately, it was determined that there was no need to enroll additional patients, and enrollment in INSPIRE was successfully concluded.

FDA and TransMedics agreed that the OCS solution subgroup would be an important adjunctive analysis to consider, since it would be the product to be marketed, if approved.

In our review of the results this morning, we will present the data in a comprehensive fashion. We will present the data for the INSPIRE cohort of the pre-specified 320 subjects as well as the combined cohort that includes the addition of the administrative extension, a total of 349 subjects.

For effectiveness, we will show the results for both the primary per-protocol analysis population as well as the modified ITT population.

In addition, we will show the results for the overall cohorts, overall arms as well as a subgroup analysis for the OCS solution subgroup, which reflects the product that will be marketed by TransMedics.

With this background in mind, I would like to invite Dr. Abbas Ardehali to review the INSPIRE trial design.

DR. ARDEHALI: Thank you. Good morning. My name is Abbas Ardehali. I am a Professor of Surgery and Medicine in the Division of Cardiothoracic Surgery at UCLA. I am a co-principal investigator for the INSPIRE trial. I have no financial interests in TransMedics, and I have never received any financial compensation.

DR. SCHWAITZBERG: Can you speak up, please?

DR. ARDEHALI: Sure. I have no financial interest in TransMedics. I have never received any financial compensation as my role for an investigator in the INSPIRE trial, but I have been compensated for my time and the travel expenses today.

I'm pleased to be here this morning to discuss the trial design. I will start by reviewing the trial's inclusion and exclusion criteria.

The donor eligibility and exclusion criteria reflect standard lung donors. Donors had to be younger than 65 years of age with normal gas exchange at final acceptance. Their lungs had no active pulmonary disease and had to be suitable for transplant using either the OCS or the cold static preservation. The donor exclusion criteria were also typical of standard practice in double-lung transplantation.

Recipients' inclusion and exclusion criteria were also typical of standard double-lung candidates. We excluded prior organ or bone marrow transplant recipients, single lung recipients, and chronic renal failure.

The primary effectiveness endpoint was a composite of all-cause patient survival at Day 30 post-transplantation and the absence of PGD3 within the first 72 hours post-

transplantation.

The non-inferiority margin for the primary effectiveness endpoint was set at 4%, which is quite conservative in comparison to other device trials, as previously described.

The safety endpoint was the mean number of lung graft-related serious adverse events through the 30 days post-transplantation. The non-inferiority margin for this endpoint was 0.07.

The lung graft-related SAEs were defined by four categories: moderate to severe acute rejection, respiratory failure, bronchial anastomotic complications, and lung-related infections.

The 30-day window was selected as it is relevant to assessing preservation-related injuries on the donor lungs, as compared to later time points which could be impacted by other variables.

There were three secondary endpoints: PGD Grade 2 at 72 hours, PGD Grade 2 or 3 at 72 hours, and patient survival at Day 30. Each secondary endpoint had its own respective non-inferiority margin, which are shown on this slide. The endpoints were tested in a fixed sequence to control Type I error.

Additional endpoints were evaluated to provide additional context for the primary results, including the incidence of bronchiolitis obliterans syndrome, ICU and hospital length of stay, and ventilation time.

As you may have read in your briefings, FDA has questioned whether the PGD assessment is consistent with the ISHLT 2005 consensus statement, and they've also questioned the imbalance in screen failures. I will address both of those issues, but first, let's review how PGD was assessed.

PGD assessment in the INSPIRE trial followed the ISHLT 2005 consensus statement shown on this slide. The clinical implementation of the consensus statement was as

follows: First, intubated patients were graded according to the table shown on this slide; second, extubated patients were graded 0 or 1 based on the chest x-ray; and finally, all patients on ECMO post-transplant were graded PGD3, except for those who received protocol prophylactic ECMO for IPAH. This PGD grading system was applied blindly, consistently, and uniformly to both the OCS and the control arms.

As you may have read in the FDA briefing document, the PGD grading in the INSPIRE trial differed from the FDA's understanding of the ISHLT consensus statement. Let me illustrate this briefly with two examples.

First, take the example of a recipient who was intubated with a P/F ratio of less than 200 with a clear chest x-ray. This was graded and adjudicated in the INSPIRE trial as PGD3, whereas the FDA would interpret the caveat to assign this patient, intubated, with a P/F ratio of less than 200, a PGD grade of 0 because of the clear chest x-ray.

Take another example of a recipient who was extubated, with a P/F ratio of less than 200, on supplemental oxygen. In INSPIRE, this was graded and adjudicated as either PGD Grade 0 or 1 depending on the chest x-ray. The FDA would've assigned this recipient a PGD Grade 3.

The INSPIRE steering committee and I stand by our clinical implementation of the ISHLT 2005 consensus statement, which was followed by the medical monitor for adjudication of PGD in this trial as clinically appropriate and valid.

As noted on this slide, the data in this and the previous slide is relevant to one of the FDA's discussion questions.

Next, let me turn to the randomization process. The INSPIRE trial randomization was designed to fit into the complex scheme of lung organ allocation for transplantation. Let me take a moment and show you how this complex process was implemented in the INSPIRE trial.

First, an eligible recipient on the waiting list would receive a potential offer. This donor offer is screened and is either declined or initially accepted. Once initial donor offer is accepted, the randomization envelope was opened and the randomization occurred. A retrieval team is sent out to the donor site to perform the final assessment and visualization of the donor lung.

At this step, one of the three outcomes may occur. One possibility is that the donor lung met the criteria and was accepted in the INSPIRE trial for transplantation.

Another possibility was that the donor lung did not meet the INSPIRE inclusion criteria, yet it was acceptable according to the transplant center's acceptance criteria and was therefore transplanted off study. This was considered a donor screen failure.

The final possibility is that the donor lung not only did not meet the INSPIRE inclusion criteria but was just not usable. That recipient remained randomized, awaiting another donor offer. If the recipient never got another suitable donor offer by the time the study is closed, that would've been a donor screen failure as well. For those who already were randomized potential recipients, they remained on the list if another donor or a lung became available.

As you can see in this schematic, randomization in this lung transplant trial was very complex.

With that background in mind, let's continue with the trial's CONSORT diagram: 407 patients were randomized in the INSPIRE trial, 199 to control and 208 to the Organ Care System. There were 15 screen failures in the control arm and 43 in the OCS arm. I will describe these in more detail in a moment. This left 184 control patients and 165 OCS patients in the modified intention-to-treat population, for a total of 349 patients.

Now let's discuss the screen failures in more detail. There were four categories of screen failures.

First, donor screen failures for eligibility; this meant that the donors did not meet the INSPIRE trial inclusion criteria at visualization, yet those donors were actually transplanted off the study. There were 17 in OCS and 6 in the control group. There appears there is a higher rate of screen failure in the OCS arm.

The second category of screen failures were for donor lungs that were not acceptable for transplantation and the patients remained on the waiting list. They were on the waiting list as the study closed. There were 4 in the control arm and 14 in the OCS arm.

The third category was logistics. There were 10 logistics screen failures in the OCS arm and 1 in the control arm. This imbalance in screen failures was due to factors like unavailability of the trained personnel or a perfusion solution or the device not ready for being deployed.

And, lastly, there were four recipient screen failures compared to two in the Organ Care System.

I acknowledge that there are more screen failures in the OCS arm compared to the control arm. We performed extensive analyses to understand what led to this imbalance. We believe multiple factors led to this number of screen failures. These include the fact that randomization occurred prior to final donor acceptance, a factor intrinsic to the field of transplantation.

In other cases, some lungs were not suitable for transplantation, and the randomized recipient on the waiting list at the end of the trial, once the trial had closed, awaiting other donor offers.

There were also some transplant logistics, several of which were due to constraints of a randomized trial.

After thorough review and extensive analyses, we could not identify a clear reason for this imbalance between the two arms. However, we did not find any evidence to

suggest that this imbalance resulted in any measurable difference in donor lung characteristics that were transplanted, favoring the OCS arm. I will show this in the next slide.

This slide compares the characteristics of the donor lungs that were actually transplanted in the two groups of the control and the OCS arm. As you can see, the donor age, P/F ratio, smoking history was nearly identical in the two groups. The incidence of abnormal findings at donor lung visualization was 26% in the control group and 36% in the OCS group.

So despite the imbalance in the screen failures, there's no evidence that better donor lungs were transplanted in the OCS cohort, which provides confidence in the study results.

With screen failures accounted for, let's discuss the trial populations. There were 184 control patients and 165 OCS patients in the modified ITT population, which includes all patients randomized and transplanted on this study. In the OCS arm there was only one lung turn-down. As a point of reference, in 2015, the rate of lung turn-down after visualization and harvesting in the United States was 6%, according to the OPTN.

The remaining patients comprised the safety population. There were 10 major protocol violations in the OCS arm and 4 in the control arm, which left 180 control patients and 154 OCS in the per-protocol population.

Let's review these pre-specified protocol violations. Patients who had a major violation were included in the mITT population but not the per-protocol population, as these violations were considered to have a potential to impact the key clinical outcomes. Four violations in the OCS arm and one in the control arm were due to findings that the donor lungs did not meet the inclusion or exclusion criteria for the trial, pre-specified criteria. Four OCS and three control violations were due to a failure to follow the

instructions for use or did not follow the protocol. And two additional violations occurred in the OCS arm where the patients were transplanted using cold static preservation rather than the OCS system.

During the Q and A session, I'll be happy to discuss the nature of these pre-specified protocol violations or screen failures which were identified by the investigators and the sites and independently reviewed and adjudicated by the medical monitor.

Finally, let me review the characteristics of the recipients in the INSPIRE trial. Again, as seen with the donor characteristics, the result of recipient characteristics did not show any evidence of bias favoring the OCS arm, whereas small differences may be observed, the recipients tended to have probably a little bit more risk factors in the OCS arm than control.

There were more female recipients in the OCS arm. The mean LAS score was 51 in the OCS compared to 48 in the control. The prevalence of secondary pulmonary arterial hypertension was 40% in OCS compared to 32% in the control. The OCS arm also had twice the percentage of patients who were diagnosed with idiopathic pulmonary arterial hypertension compared to control group.

In conclusion, the INSPIRE trial is a prospective randomized controlled trial which was successfully implemented in 21 international academic lung transplant centers in the complex field of lung transplantation.

PGD assessment followed the clinical implementation of the 2005 ISHLT consensus statement.

After a thorough review of the data, the imbalance in the donor screen failures did not appear to lead to any measurable bias favoring the OCS arm.

The INSPIRE trial represents the largest body of prospective clinical evidence supporting the use of ex vivo lung perfusion in lung transplantation.

Next, I'll ask Dr. John Wallwork, the INSPIRE trial medical monitor, to provide some

clarification of the adjudication of the PGD and the adverse events.

DR. WALLWORK: Thank you. Good morning. I'm John Wallwork. I may be known to some of you, but I will give you some relevant background information for the others.

I have more than 30 years experience in heart, heart-lung, and lung transplantation. I was the chief resident at Stanford Hospital when Bruce Reitz performed the first successful heart-lung transplant in the world in 1981. And I performed the first successful heart-lung transplant in Europe and the world's first heart-lung-liver transplant.

I was director of the transplant program at Papworth Hospital, one of the most active heart and lung transplant services in the world, until 2006 when I ceased any clinical involvement in transplantation. And to be clear, I retired entirely from clinical practice in 2011, prior to the beginning of the INSPIRE trial, and thus have no institutional bias. I am the Emeritus Professor of Cardiothoracic Surgery at Papworth Hospital and Cambridge University in the UK, and I'm now chairman of the board of Papworth Hospital. I was a founding member of the International Society for Heart and Lung Transplantation and, as you can see, was its previous president.

As medical monitor, I worked with extensive accumulated independent knowledge of lung transplantation, and this enabled me to adjudicate impartially, consistently, and with rigor and without prejudice within the predetermined protocol definitions across all patients in this trial, blinded to the study groups.

I served two roles for the INSPIRE trial. First, I was the independent medical monitor where I adjudicated PGD scores according to the International Society guidelines of 2005 and as set out in the protocol. I implemented this in a blinded and consistent manner for both study groups.

I also adjudicated all serious adverse events according to the protocol definitions. I made no changes to the protocol safety endpoint definitions. This process was

implemented in a blinded and consistent manner for both study groups.

I did have access to additional source data to clarify PGD and adverse event adjudication, again in a blinded manner.

I was also a member of the DSMB, chaired by Professor Sonett, which did not conflict with my role as medical monitor since the DSMB only reviewed adjudicated, unblinded group safety data and thus did not prejudice my PGD score adjudication. I did not take part in any data analysis.

I'd like now to invite Dr. Warnecke to the podium to present the results.

DR. WARNECKE: Thank you. I'm Gregor Warnecke. I am the Vice Chairman of the Department of Cardiothoracic Surgery of the Hannover Medical School and the Director of the Heart and Lung Transplant Program there. Hannover Medical School maintained the largest lung transplant program worldwide in 2014, '15, and '16. I'm also the co-principal investigator of the INSPIRE trial. I have no financial interests in TransMedics, and I did not receive any financial compensation from TransMedics for my role as an investigator in the INSPIRE trial or for my time to present here today.

I am pleased to be here this morning to present the results of the trial. My presentation of the INSPIRE trial results will follow this outline. First, I'll present OCS perfusion parameters and oxygenation on the OCS. Then I'll present the composite primary effectiveness endpoint, followed by the individual components of the primary composite endpoint at the adjunct analysis. Then I will present the remaining secondary endpoints, safety, and additional clinical endpoints.

I'm going to start with the OCS perfusion parameters. These are the definitions of the cross-clamp and ischemic times used in the trial. The cross-clamp time was the time from aortic cross-clamping in the donor to the pulmonary artery cross-clamp removal in the recipient. The ischemic time is the time the donor lung was not perfused. Let me illustrate

the practical clinical implementation of these definitions in the INSPIRE trial from the time the lungs were retrieved from the donor until they are transplanted into the recipient.

In the control arm, cross-clamp and ischemic times are identical since the lungs are never perfused with oxygenated blood during preservation. In the OCS arm, the ischemic time is limited to small windows of time during harvest and instrumentation on OCS and during final reimplantation into the recipient. Other than that, the donor lung is perfused with oxygenated blood-based perfusate.

Now, let me share with you the results from the INSPIRE trial about these two important clinical parameters in lung transplantation.

The OCS significantly reduced the ischemic time on both donor lungs, compared to the control arm. This significant reduction of ischemic time was achieved despite significantly longer total cross-clamp times in the OCS arm. This is an important clinical benefit since, for the first time, we have a preservation technology capable of reducing the injurious ischemic time on the lung allograft, regardless of the travel distance. This also could enable for better logistical management of the transplantation.

During OCS perfusion, we monitor vascular resistance and airway pressures as signs of stability of perfusion and donor lung condition. This graph demonstrates the OCS Lung perfusion parameters and airway pressures actually decreased throughout the OCS perfusion, indicating stability and good preservation.

This graph compares the donor lung oxygenation capacity measured by the standard P/F ratio at the end of OCS preservation to the final P/F ratio at the time of donor lung retrieval. These results show that the OCS was able to maintain or even slightly improve lung condition and oxygenation capacity throughout the preservation period.

Next, I'll present the composite primary effectiveness endpoint. Here are the data based on the trial cohort of 320 patients on the left as well as the combined cohort of 349

patients on the right. We see that the OCS arm met the non-inferiority test in both cohorts. When we assess the OCS solution subgroup, these results were validated and further improved, reassuring that the OCS has met the non-inferiority test for the primary effectiveness endpoint for INSPIRE.

This forest plot summarizes the bar charts I just showed in the previous slide for all analysis populations. This figure shows both point estimates and percent differences between the two study arms for different study populations. Percentages to the left of zero indicate that OCS performance was better than control. For example, the -9.1% difference at the top means that 9.1% more OCS patients met the primary endpoint than control patients. The red dashed line shows the 4% margin for non-inferiority.

As you see in the mITT analysis, even though OCS performed 2.1 to 3.8% better than control, it did not meet the 4% non-inferiority test due to the narrowness of the margin.

As was explained earlier, we also performed post hoc subgroup analysis of those patients in the OCS arm where lungs were preserved specifically with OCS lung solution. As you can see, the differences between the arms all increased, and non-inferiority was achieved in all populations.

Now, I will present the individual components of the primary composite, starting with short-term survival.

This slide summarizes 30-day survival in the combined cohort for both per-protocol and mITT populations. The blue column is the control group. The red column is the OCS arm showing lower 30-day survival.

This graph represents the 30-day survival reported in the 2014 annual report for the Organ Procurement and Transplant Network, summarizing the status of all lung transplant recipients in the U.S. As you can see, the survival for the OCS group is quite similar to the literature, while the survival in the control group is higher.

Looking at the causes of death through Day 30 in detail, there were four deaths due to lung graft failure and seven due to other causes unrelated to the lung graft. Quite a few of these patients were actually in the normal ward or at home at the time the cardiac or vascular event occurred, supporting that they were not lung graft related.

Upon a closer examination of the survival data, we realized that only assessing survival at Day 30 was an incomplete assessment of early post-transplant outcomes, since several patients suffering from severe transplant-related complications lived past 30 days, maintained on mechanical ventilation in the intensive care unit, but died prior to being discharged from their initial transplant procedure hospital admission.

Therefore, we did an analysis to assess short-term survival at Day 30 and during the initial transplant hospitalization. In this analysis, it becomes apparent that early mortality is similar in the control and OCS arms, with 12 early deaths in the OCS and 12 early deaths in the control arm. More specifically, there were twice the number of lung graft-related early mortalities in the control arm as compared to the OCS arm.

Using this comprehensive assessment of overall early mortality, we see that the early survival rates between OCS and control were completely similar. This analysis should help to address FDA's discussion question concerning the imbalance in 30-day mortality. As you can see, the difference observed at 30-day disappears when you consider 30-day mortality plus mortality during the initial hospitalization post-transplant.

Now I will present the second component of the primary composite effectiveness endpoint, which is the rate of primary graft dysfunction Grade 3 within the initial 72 hours after lung transplantation.

The left panel is the original INSPIRE cohort, and the right panel is the combined cohort. The OCS arm was associated with a significant reduction of PGD Grade 3 within 72 hours in both cohorts. It is important to note that the control arm in INSPIRE had a 30%

incidence of PGD3 within 72 hours, which is consistent with published literature that Dr. Loor discussed earlier. PGD3 was reduced in the OCS arm to 18 or 19%, respectively.

The significant reduction of PGD3 was further improved in the OCS solution subgroup. This is an important clinical finding of the INSPIRE trial, since this data represents the first evidence of a new therapy that can reduce the incidence of the PGD post-lung transplantation.

Since 30-day mortality incompletely represents the real burden of early mortality, we performed a post hoc adjunct effectiveness analysis composed of 30-day survival and in-hospital survival and freedom from PGD3 within 72 hours.

Looking at the left panel, which is the original INSPIRE trial cohort of 320 patients as well as the right panel with the combined cohort, we see that the OCS arm was shown to be non-inferior as well as superior to control.

This forest plot shows the results for all analysis populations in both cohorts. This post hoc adjunct effectiveness analysis supports non-inferiority in the per-protocol population as well as in the mITT population. Again, the differences were larger when looking at the OCS solution subgroup, which is the solution that will be used and marketed once the product is approved.

Next, I'll present the remaining secondary endpoints, starting with the PGD3 at 72 hours.

The incidence of PGD Grade 3 at 72 hours was similar between the groups and was low overall, very low overall. Non-inferiority was achieved in most of the populations analyzed. These data address the FDA's Discussion Question 1 relating to the initially approved primary composite endpoint, of which one component was PGD3 at T72. This is to clarify that failure of the initially approved composite endpoint to reach statistical non-inferiority was not driven by PGD3 at 72 hours; rather, it was the imbalance in 30-day

survival. However, as I described earlier, the early survival results were similar between arms when we evaluated a more comprehensive definition that included in-hospital mortality.

The final secondary endpoint was the rate of PGD Grade 2 or 3 at 72 hours. Non-inferiority was not achieved in the analysis of the overall OCS arm. Non-inferiority was achieved in most of the analysis populations for the OCS solution subgroup.

Next, I will present the safety results, starting with the safety endpoint. The OCS Lung System met its safety endpoint, which was the mean number of lung graft-related serious adverse events. These events were composed of acute rejections, respiratory failures, bronchial anastomotic complications, and major pulmonary-related infections.

As you can see, the overall rates of lung graft-related SAEs were almost identical, with an incidence of approximately 24% in both arms. The mean number of events was 0.29 events in the control arm and 0.26 events in the OCS arm. There was a somewhat higher rate of bronchial anastomotic complications and major pulmonary-related infections in the control arm. And as noted by the FDA in one of their discussion questions, there was a slightly higher rate of respiratory failure events in the OCS arm.

While none of these differences were significant, and the overall profile of lung graft-related SAEs was similar, we evaluated the survival profile of the patients who experienced an SAE for respiratory failure to further evaluate the implications of that observation.

Respiratory failure occurred in 16 control patients and 23 OCS patients. As seen on this graph, the OCS arm had better survival at all time points for those who had respiratory failure as compared to the control arm. These results further address the concern raised by FDA about the small difference in the incidence of respiratory failure observed between the two arms.

The overall safety profile was quite similar between the OCS and the control groups. Mortality at 24 months was similar between the two arms. Furthermore, the rates of related adverse events were comparable between the two arms.

Finally, I will present the additional clinical endpoints. The OCS was associated with trends for shorter ventilation times, shorter length of an intensive care unit stay, and shorter initial hospital stays, as shown in these three graphs.

Looking at longer-term outcomes, here we see the probability of freedom from bronchiolitis obliterans syndrome through 2 years in the Kaplan-Meier curve. These probabilities are quite high in both arms compared with historical registry data, but it shows an encouraging result indicating a possible higher BOS-free probability in the OCS group at 24 months. This endpoint will be further examined in TransMedics' proposed postmarket study, which will be discussed in more detail in a few moments.

In conclusion, the INSPIRE trial demonstrated the safety and effectiveness of the OCS Lung System. The primary effectiveness endpoint and the safety endpoint were met.

Additionally, the trial demonstrated a significant reduction in PGD3 within the first 72 hours post-transplantation.

INSPIRE also demonstrated a significant reduction of ischemic time on donor lungs.

With these additional benefits, we did not observe additional safety risks compared to the control group.

And lastly, we observed favorable results with BOS at 2 years, which will be further evaluated in a post-approval registry.

Thank you for your attention, and I will now turn the presentation back over to Dr. Hassanein.

DR. HASSANEIN: Thank you, Dr. Warnecke.

I would like now to take a few moments to review the proposed training program or

the training program and our proposed postmarket or post-approval study.

As a clinically driven organization, clinical training and support is very important for TransMedics, and we've built a dedicated team and resources to be able to support our clinical users and commercial users worldwide. TransMedics has a dedicated clinical training facility equipped with the latest surgical and diagnostic equipment to replicate organ retrieval environment. In our facility, we've conducted training for 86 global academic transplant centers, and we have trained more than 400 transplant clinicians, transplant surgeons, and healthcare professionals across all our three organ platforms.

This is a photo of one of our three laminar-flow operating rooms designed to replicate the donor surgical retrieval environment and to demonstrate how OCS technology fits into the flow or the process at the donor site.

This is our dedicated perfusion lab designed to enable full clinical and functional and metabolic assessment of the donor lungs with those in the Organ Care System. This lab is equipped with blood gas analyzers, full fiber optic bronchoscopy equipment, and other relevant clinical diagnostic equipment routinely used for assessing donor organs prior to transplantation.

Our clinical training program has been refined through years based on the firsthand experience and learning from our ongoing pivotal studies. Let me summarize these components. There are three components to it.

First, every new clinical center must undergo a 2- to 3-day initial hands-on clinical training and certification program at our facility. This includes full surgical wet lab instrumentation, management, and assessment of the donor organ on the OCS. In addition, it covers troubleshooting scenarios and theory of operations of the system.

Two, our Organ Care System training and support software application that every center leaves our facility, our training program, with an iPad application locked and loaded

with this software application. This is designed to serve as a quick refresher that could be used by the retrieval team right at the point of retrieval, with training videos and checklists to ensure adherence to the use model.

Finally, we have a 24-by-7 phone and text messaging hotline to assist and address any questions from users worldwide during the use of the OCS system.

Next, I would like to discuss our proposed post-approval study plans. We have proposed a two-part post-approval study plan to continue to build clinical evidence for the OCS Lung System in the postmarket setting. Part 1 includes a long-term follow-up of INSPIRE transplanted patients for up to 5 years. Currently, we have 2 years; we're proposing an additional 3-year follow-up. Part 2 includes the establishment of an OCS thoracic organ perfusion registry to collect clinical outcomes for new OCS cases. Let me provide you a summary overview of these two parts.

Our goal for Part 1 is to continue to monitor and assess the impact of OCS lung preservation on the incidence of BOS and survival up to 5 years for all INSPIRE transplanted patients. We will collect BOS diagnosis and survival data from all INSPIRE trial patients for an additional 3 years, given as 5-year follow-up.

Part 2 is the establishment of an OCS thoracic organ perfusion registry that will collect data from the first 150 new OCS lung transplant patients for 5 years to expand clinical evidence for the OCS Lung System in the post-approval or postmarket setting. We propose that data entry be mandatory for new centers. We are planning to utilize an academic steering committee to help oversee the registry as well as we're planning to invest in implementing independent monitoring of the data to maintain high quality of the data being entered into this registry. In addition to long-term survival and incidence of BOS, we will collect PGD grades comprehensively through the initial 72 hours post-transplant.

Thank you. I'll now turn the presentation over to Professor Van Raemdonck to close our presentation.

DR. VAN RAEMDONCK: Thank you, and good morning. I'm Dirk Van Raemdonck. I'm a professor at the University of Leuven and the Director of the Transplant Center at the University Hospitals of Leuven, Belgium. I was also the co-chair of the ISHLT PGD working group, both in 2005 and in 2016.

Like my other colleagues, I have no personal financial interests in TransMedics, and I have not received any financial compensation from TransMedics for my role as an investigator in the INSPIRE trial or for my time to cross the Atlantic and to present here today.

I'm pleased to have the opportunity to share my clinical perspectives and benefit-risk assessment of the OCS Lung System.

We have witnessed significant clinical advancements in surgical techniques and postoperative care for lung transplantation. However, we have essentially made no progress in preservation techniques. For the last 30 years, all we have had is cold static ischemic storage. Ex vivo lung perfusion is a paradigm shift for dynamic lung preservation and assessment and has become a new promising technique for all solid organs.

After a visit to Stig Steen's lab in Sweden in 2000, the father of EVLP, our group started experiments in our own lab, and we presented these results in 20 human lungs already in 2004 at the ISHLT meeting in San Diego. It was at this meeting where we first introduced the term EVLP, or ex vivo lung perfusion.

Now, to bring this to clinical practice, I have always stated that we needed a clinical device to change the complex and non-standardized laboratory setting into standard practice. OCS represents the technical solution. OCS is a state-of-the-art ex vivo warm perfusion and ventilation system that allows physicians to preserve the lungs in a near

physiologic state while monitoring these organs during the entire transport and preservation process.

The OCS enables new optimization and assessment capabilities that are not possible with cold storage. And as shown by Dr. Warnecke, the donor lungs were well maintained on the OCS system, and they displayed stable or even improving perfusion parameters and oxygenation. And clinically, that will translate into improved quality of donor lung preservation and improved clinical decision making, since we can now monitor lung conditions up to the point of transplantation.

One of the greatest benefits of the OCS system is its ability to minimize the time-dependent limitations of cold ischemic storage. As Dr. Warnecke presented earlier, the OCS Lung System in the INSPIRE significantly reduced ischemic time compared to cold storage, despite longer cross-clamp times. And these benefits of reduced ischemic times, regardless of increased cross-clamp times, will enable longer distal retrieval of donor lungs which could help better utilization of available donor lungs and could improve the overall management of transplantation logistics at our transplant centers.

The OCS Lung System is the first technology to demonstrate a significant reduction in the most severe form of primary graft dysfunction. And in clinical practice, we see the devastating effect of PGD on our lung transplant patients. In today's practice, lung preservation is not only an icebox, it is also a block box because one of every three patients we transplant will suffer from the most severe form of primary graft dysfunction at some time point within the first 72 hours.

And as you have heard today, these patients are at the higher risk of mortality, have a higher risk of long-term complications, and face a more prolonged recovery period with longer ventilation time, ICU stay, and hospital stay. And this reduction would offer the patients the possibility of achieving better short- and long-term outcomes following

transplantation.

And, finally, the encouraging 2-year BOS results in the OCS group in this trial are consistent with the data presented earlier by Dr. Loor this morning, that PGD3 at any time point is linked to BOS.

TransMedics has committed to studying the potential long-term benefits of the OCS in the post-approval setting.

Turning to a risk assessment of the OCS Lung System, the INSPIRE trial demonstrates reasonable assurance of safety for the OCS system. And I'll begin with an observation that based on my experience, it is rare to see a new technology become available with both significant benefit to patients and also a safety profile that is so similar to the current standard of care.

The OCS system met its safety endpoint, and the rates of specific types of lung graft-related serious adverse events were similar between the trial arms. Yes, 30-day mortality was slightly higher in the OCS arm, but this was due primarily to surgical and cardiac events unrelated to the lung graft.

Patients treated with the OCS Lung System demonstrate similar mortality in the initial post-transplant hospitalization period and at 12 and 24 months compared to cold storage. Overall, the device has a favorable safety profile through 2 years.

In summary, INSPIRE successfully met its primary effectiveness endpoint, and the OCS performed similar to or better than control on most of the effectiveness measures.

The OCS Lung System minimizes ischemic injury by perfusing the lung with warm oxygenated blood. And in doing so, the OCS system significantly reduced the incidence of PGD Grade 3 and extended the amount of time the lungs can remain healthy outside of the body.

Furthermore, the system allows the physician to optimize and to monitor the health

of the donor lungs from the moment they are placed in the system until the point of transplantation.

And with all of these benefits and no additional safety risks, my opinion is that the OCS system demonstrated a positive benefit-risk profile.

In conclusion, Panel members, based on our collective clinical experience and the totality of the data presented, it is clear that the OCS Lung System is a paradigm shift advancing our field of lung transplantation. And this is an important first step towards further potential advancements in our clinical field.

If approved, the OCS system will be further studied for its ability to improve long-term viability of donor lungs and also increase the availability of lungs that are currently wasted due to the limitations of cold storage. And this would reduce mortality of our patients on the waiting list. That's why providing this safe and effective technology to patients and clinicians also in the United States now is critical to advancing the field of lung transplantation.

Thank you to all 21 investigators for concluding this important and unprecedented trial.

I will now turn the lecture back over to Dr. Hassanein to address the Panel's questions.

DR. SCHWAITZBERG: I would like to thank the Sponsor for their on-time presentation and as well as all the representatives that spoke.

I would like to ask the Panel for an opportunity to ask any brief and clarifying questions. You'll have an opportunity, also, to ask the Sponsor questions -- I'm going to go around the room -- with deliberations. And I will start with Dr. Hammon. If you don't have any questions, just take a pass and we'll move on, and we'll go this way and then back, and I'll ask any concluding questions.

Dr. Hammon.

DR. HAMMON: Very nice presentations. It was clear that there was some advantage to using your system in terms of long-term avoidance of BOS. However, that plus some of the other advantages were statistically significant but still not tremendously different. So I would like to ask you what is the increase in cost using your machine to the overall transplant procedure?

DR. HASSANEIN: Thank you, Dr. Hammon. The benefit of the Organ Care System has been, as has been shown from my speakers, the reduction of primary graft dysfunction Grade 3, the potential impact on reducing the cost of ICU stay and hospital stay; these are all clinical and economic benefits, the potential of the Organ Care System technology. The actual cost of the OCS is $45,000 per procedure, but I thought that the topic of discussion today is the assessment of safety and effectiveness and benefit-risk for the technology. But the answer is $45,000 additional cost per procedure. But there's additional cost savings associated with improved clinical outcome in reduction of primary graft dysfunction.

DR. SCHWAITZBERG: Great. Questions, further questions?

DR. FISHER: A quick comment, please.

DR. SCHWAITZBERG: Dr. Fisher.

DR. FISHER: Thank you very much. I'm in agreement here in that we would not necessarily take the cost of the procedure into consideration for the evaluation of the PMA. So I do understand where your question is going, but for the evaluation of the PMA itself, that would not be something that FDA would take into consideration.

DR. HASSANEIN: Thank you, Dr. Fisher.

DR. VAN BERKEL: Thank you. I just have a couple very -- these are very specific questions, and I apologize if it's a little pedantic, about some of the major protocol violations. There were four patients that I was able to find in the appendix that were

talking about their major protocol violations, and I'm just curious as to what happened in those cases.

So, for example, on Patient 34003, there was a failure to follow the instructions. Essentially, it looked like there was someone who was not very familiar with the OCS machinery and wasn't able to locate the "on" device and didn't wrap the lung appropriately, and I'm just wondering, did that person then get that lung transplanted as cold storage, or was that lung thrown away, or what happened there?

DR. HASSANEIN: No, none of the protocol violations were thrown away. This lung was actually transplanted into the recipient.

DR. VAN BERKEL: Okay. So there were a couple others in the appendix where it said, specifically, the patient was transplanted using cold storage, and the ones that I was curious about did not say that. All of the protocol violations were then transplanted, essentially were transplanted either on the OCS protocol or by cold storage?

DR. HASSANEIN: That is correct.

DR. VAN BERKEL: Okay, thank you.

DR. SCHWAITZBERG: Sasha.

DR. KRUPNICK: Yeah, just two quick questions. One, I guess, that's not part of this data, but obviously looking at this from a clinical point of view, the big utility and then talk about it, is extending the ischemic time past what you could tolerate with standard, like 12 hours, 18 hours. You know, having recently moved to the coast, I can tell you that's kind of a big problem for us. I know it's not part of any of this data, but is there any data that can be considered of extending ischemic time past what would be clinically acceptable for cold storage?

DR. HASSANEIN: There is an ongoing EXPAND lung trial that is specifically looking at these additional potential indications, and we're working very hard to conclude that study,

and hopefully, we'll be back in front of the esteemed Panel members to present that. However, as I mentioned earlier, the OCS Lung System has been available in Europe for several years, and to answer that specific question, I'd like to invite Dr. Van Raemdonck to present his own clinical experience outside of the INSPIRE trial from using the system in Leuven for potentially addressing the specific question about extended cross-clamp time.

DR. VAN RAEMDONCK: Thank you. Indeed, we have used the technology to transplant patients with combined liver and lung transplants whereby, in three patients, we first transplanted the liver on ice while the lungs were preserved for 12 hours on the OCS device, and in doing so, we were able to transplant the patient, who had no clotting because of liver failure, and the patient was successfully transplanted. And we've published that as a case report in the *American Journal of Transplantation*.

DR. KRUPNICK: What is the PGD grade in that? I know it's one patient.

DR. VAN RAEMDONCK: If I recollect correctly from my mind, this patient did not have any PGD Grade 3.

DR. SCHWAITZBERG: Great. Mr. Stammers.

MR. STAMMERS: Thank you. A very quick question: One or more of the failures that has been reported was dealing with training issues and the absence of appropriately trained clinicians to offer OCS. Who have you identified as the individuals who are going to be responsible for manning the machine, and what are the minimal qualifications that you have?

DR. HASSANEIN: Sure. Please allow me to address that question in two parts. The first part, the specific failures that's been identified, it was actually screen -- logistics screen failure because the trained personnel were not available, and most of these cases occurred when the second donor or third donor offer occurred, and it occurs at any time, and it happened that the trained personnel were not available. So it was not a failure. These

lungs were transplanted, and the patient received the lung transplant.

To address your second question, the way we've been approaching this, to date, in more than 86 transplant institutions for all three organs, is we really asked the institution to identify the appropriate retrieval team, and we don't like or we don't request or we don't recommend changing the construct or the background of the retrieval team. This is why we've modified our training program to make it as broad as it is and develop this iPad application with live training videos so that anybody that goes on organ retrieval today has been using the OCS and many of our European users have been implementing this throughout the institution.

Some institutions, however, require that an additional perfusion service is to be provided, and it has been integrated very nicely. Some of these institutions are here in the U.S. as a part of our clinical trial program. What we do is, to make it really center specific, the center tells us who is the retrieval team that needs to be trained, and our job is to train them, certify them, and maintain the quality system of that training program.

MR. STAMMERS: Very quick, one more: Very quickly, there are states that have licensure for what individuals are able to run artificial lungs, artificial pumps, such as this device has, and I wonder, with what you just described to us, if you would be in violation of training individuals without specific -- in those states that are licensed, specifically for perfusion, to operate these devices.

DR. HASSANEIN: The OCS and perfusion systems are not under the -- at least as we know it today, ex vivo organ perfusion is not under that umbrella, given that it's not a human-sustaining or -- you know, the EVLP today is conducted, you know, without that -- under that specific umbrella. It's not under the cardiopulmonary bypass. My wife is a perfusionist, so I'm very familiar with the rules.

DR. SCHWAITZBERG: Great. Dr. O'Connor.

DR. O'CONNOR: I have two questions. Can you hear me? My first question is about PGD scoring. One of the problems with using the 2005 criteria is, in the modern era, many patients postoperatively, who have this respiratory failure, are noninvasively ventilated; you ventilate them with bypass where we use high-flow nasal cannula. If you use the not intubated criteria, the highest PGD score that person could have would be 1. But in many centers, we noninvasively ventilate or use high-flow nasal cannula in such people who are fundamentally in respiratory failure.

And so my question is how did you score people who had noninvasive ventilation? Did you identify them separately in your database? And did any of your patients get high-flow nasal cannula? That's my first question.

DR. HASSANEIN: Sure.

DR. O'CONNOR: My second question is your data suggests a dramatic reduction in ischemic time and a dramatic prolongation in the time to implantation and a lower rate of PGD. But at 2 years, you've got only a 3% reduction in BOS, which is, I think, less reduction in BOS than you would've predicted on the basis of the dramatic reduction in PGD 2 and 3.

DR. HASSANEIN: So let me address question number one, which is related to PGD grading. And during the interactive review process with this PMA, we heard the concerns, and we identified eight patients in each group that had $FiO_2$ greater than 30%, and we looked at those, and if you even grade them all as PGD3, it does not change the conclusion of the primary effectiveness endpoint. So that's to answer question number one.

To address question number two, if you'd be so kind to repeat that question.

DR. O'CONNOR: Sure. So you have a dramatic reduction in your ischemic time and a significant reduction in your PGD1, 2, 3, but only a 3% reduction in BOS at 2 years.

DR. HASSANEIN: Correct. We performed some sensitivity analyses looking specifically at this issue, correlating ischemic time and BOS and also PGD3 within 72 hours

and BOS. And I'd like to invite Dr. Warnecke to address that question.

DR. WARNECKE: Yes, you're right. And the difference is not statistically significant. However, most transplant pulmonologists will say the right point of time to evaluate the real difference is only after 3 years or more after transplantation. So we have 24-month follow-up data now, and all we see is a trend of already 3%. So if the trend persists and the gap widens at 3 years, which is something I would expect, then that would be probably the right time to really say this. Until 24 months, we have a BOS-free survival of way above 80% still, so that's probably too early to judge the real difference.

DR. HASSANEIN: And, Dr. O'Connor, if you --

DR. O'CONNOR: Just one quick comment, and that is that if you look at the data presented by Dr. Loor of the various peer-reviewed studies, I mean, your rate of BOS is lower than in any of those studies in both groups.

DR. HASSANEIN: We acknowledge that, yes. That's why Dr. Warnecke stated that in his presentation. Actually, Mr. Chairman, may I --

DR. SCHWAITZBERG: One minute.

DR. HASSANEIN: One minute. Can you please put CB-2 back again? The last --

DR. SCHWAITZBERG: The following slide, CB-3.

DR. LOOR: I just want to point out one comment because we did --

DR. SCHWAITZBERG: Reintroduce yourself for the transcriber.

DR. LOOR: Oh, sorry. Dr. Gabriel Loor of Baylor College of Medicine, Baylor St. Luke's Medical Center in Houston.

So we were struck by that finding as well, and it was -- this was the first prospectively collected PGD3 scores and BOS scores, so there may be some differences when we compare it to the retrospective data.

I just want to point out two quick slides, as we looked at this a little bit more in

depth. If you look at the ischemic times, cold ischemic times, as they go to 5 to 6.5, then greater than 6.5, you do see an increase in PGD3.

Then, what I'd like to do is show you the next slide. This is a little bit more interesting. It kind of gets to the question that you pointed out which is, if you look at these different quartiles of ischemic times, the green line represents -- or the black line, rather, represents ischemic times of 1 to 5 hours, so the shorter ischemic times. As we start getting into cold ischemic times greater than 8 hours, which is the red one, you see a significant drop-off in BOS-free survival. So I think this is consistent with Dr. Warnecke's hypothesis that we will probably see the two arms continue to spread with time.

DR. SCHWAITZBERG: Great. Just remember to introduce yourself before your questions, Dr. Connor.

DR. CONNOR: Jason Connor.

So, you know, one of the -- I think -- struggles, right, is the endpoint really treats death the same as it treats PGD3, either within 72 hours or exactly at 72 hours. And one of the things you said at the beginning was "any PGD within 72 hours matters." So do you have a plot essentially exactly like the one you just showed that shows whether a patient never had a PGD3 -- the last one was, say, at 24 hours, 48 hours, or 72 hours -- then by either survival or by BOS? Because that would really allow us to see if PGD3 matters.

DR. HASSANEIN: Thank you. This slide, I think, addresses that question. This is looking at PGD3 within 72 hours, and first, a patient who had PGD3 at any time points within 72 hours versus patients who never had PGD3 or patients who did not have any PGD greater than 1 throughout the INSPIRE trial, showing BOS-free survival. So we're --

DR. CONNOR: Right. So I think what I'm trying to get at is really the transient ones, right? When you change, and your analysis essentially goes from not significant to significant with the protocol update, the difference is people who had PGD, say, at 0 or 24

but not by 72. So that's what I would like to understand is these transient ones --

DR. HASSANEIN: Sure.

DR. CONNOR: -- who kind of flip-flop at the point of your protocol update.

DR. HASSANEIN: Sure. Let me show you another slide that might help address that question. This is a slide where we looked specifically --

DR. CONNOR: So let me say what I'm asking for, and I thought I did --

DR. HASSANEIN: Go ahead, go ahead.

DR. CONNOR: -- but rather than guessing, so you can maybe do this after lunch, then --

DR. HASSANEIN: Sure.

DR. CONNOR: -- is to show a Kaplan-Meier plot with patients who, their last one was, say, 0, who had it at 1 and then not again, I mean 1 day, 24 hours.

DR. HASSANEIN: We will attempt --

DR. CONNOR: Okay.

DR. HASSANEIN: If you allow us, we'll attempt --

DR. CONNOR: Okay.

DR. HASSANEIN: -- to get that Kaplan-Meier after lunch.

DR. CONNOR: All right, thank you.

DR. HASSANEIN: Thank you.

DR. SCHWAITZBERG: We'll come back to that after lunch.

MR. THURAMALLA: Naveen Thuramalla.

Two questions. Thank you for the excellent presentation. From the presentation, I learned that you had 800 successful transplantations already done globally. How does the significant adverse events risk profile compare to the one in the INSPIRE trial? And do you have any long-term data from those 800 patients?

DR. HASSANEIN: Thank you for the question. I wanted to just clarify that the 800, that covers lung, heart, and livers. So it's across all our three organ platforms. We have long-term data that is published on the organs that's been approved outside of the U.S. longer. We have 5-year data on the heart. The lung, we still -- the vast majority of the lungs are a part of our INSPIRE trial, so our publication for the 3-year outcome in INSPIRE is under review right now. So we hope that longer-term outcomes for the lung specifically will be coming as a part of our proposed post-approval plan. But for the heart, there's 5-year outcomes showing that the OCS 5-year outcomes are favorable and either as good as or better than control. And the liver is our newest program, so we don't have long-term outcomes on it yet.

MR. FRANKEL: Naftali Frankel.

Thank you very much. Going back to the screen failures just for a moment. Obviously, the control being 15 and OCS 43, just specifically regarding the logistics, which was 1 in the control and 10 in the OCS, and overall, are you able to identify -- I mean, there was some talk as far the learning curve. Did you analyze that further to determine what exactly that learning curve looks like by center where the different procedures were being performed?

And also the longer-term data that you showed on CO-84 and CO-80, regarding respiratory failure and BOS for the 12-month and 24-month data, do you have, correlating to that, the overall survival data of those patients?

DR. HASSANEIN: Let me address the first question related to logistic screen failure. So we looked into that matter very obviously in detail, and let me clarify. All logistic screen failures in this slide, all of these lungs have been transplanted successfully into our recipients, so none of these lungs were wasted.

When you look at the specifics of the logistic screen failure, you will find that the

vast majority, 7 out of the 10 logistic screen failures, occurred at a second or a third donor offer. Let me explain that. What does that mean clinically or practically? These patients, there had been a previous offer for them before. They went out, and the lung was rejected for transplant altogether. So now that recipient, the priority is to get that recipient transplanted quickly. So a potential second donor arrived, but it occurred, let's say, over a holiday, over a weekend. The vast majority of those trained personnel for the trial were not available, so obviously, the priority is to get that lung and transplant it to the recipient.

There were some other extraneous factors. For instance, in outside of the U.S., there's donor retrieval where a potential donor arrived for that recipient, but it was outside of the zone. So, again, the priority will go to "get the lung to the recipient."

So these issues have actually significantly decreased. We're looking at data that are 4 years old now, or 3 years old. As more and more centers have become more comfortable and more trained on OCS, we're seeing less and less -- especially in the area of unavailable trained personnel, many of the centers now have OCS, especially outside of the U.S., have it integrated into their team, so there is less and less logistic screen failure due to not available trained personnel.

MR. FRANKEL: So you don't anticipate that challenge of that discrepancy to be brought in or at least the same outside the realm of the clinical trial?

DR. HASSANEIN: We certainly don't expect that, given that as we're currently involved in our second criteria, lung program, and we're seeing literally significantly lower rates of logistic screen failure. Just to give you an example, we have one so far in a study that involved 80 patients. So we're seeing significant reduction of that because more and more centers are training more and more personnel, so they're not limited to one or two or whatever, that one retrieval team. So we don't expect that to change post-approval. But even just to provide comfort, post-approval, all of those lungs were transplanted. These are

not wasted lungs. Even for any unforeseen situation, even if it happened -- sorry.

MR. FRANKEL: Just in terms of the survival data.

DR. HASSANEIN: I'm sorry?

MR. FRANKEL: In terms of the survival data.

DR. HASSANEIN: If you don't mind, I'll get that data after the break.

MR. FRANKEL: Thank you.

DR. HASSANEIN: Thank you.

DR. SCHWAITZBERG: Ms. Barnes.

MS. BARNES: First, I want to thank you for taking the time and effort over these years to investigate improving --

DR. HASSANEIN: Thank you.

MS. BARNES: -- methods for transplantation. And I want to mention that I appreciate the technology that's used in transplant and the knowledge and skills that are necessary for the teams that do the work.

So regarding your training program, how will you, you know, increase the number -- I think you said 400 were currently trained. How will you increase that number? As people get up to speed, as the technology moves forward, how will you improve that training over time? So as your technology could change, as technology in this space changes, how will you update that information for those trainees over time? And I understand that you said they were certified. Is there an ongoing certification, or is it a one-time certification?

And during the time of transplant, which, as you know, can be extremely stressful, there's limited time, there's a lot of detail that has to be looked at. Are there -- I noticed you have real-time 24-hour/7-day-a-week hotlines, and you also said that your iPads are loaded and ready. You know, in a situation where that doesn't work, is there a real-time videoconferencing or other tool that allows the teams to communicate better, especially in

a very difficult situation?

DR. HASSANEIN: Sure. So there are three segments to the question. The first, we've learned already from the ongoing trial to design and continue to refine the training program. The area that is going to be continuously improved is the iPad application because we've seen significant improvement in users following the use model, especially with the addition of the videos. So we expect that to continue to be refined and continue to be scaled as needed.

Relating to the second point, a 24-by-7 hotline, we're actually very surprised that it's no longer being as actively used since we've introduce the iPad. However, again, with the centers we trained, we always give them that option exactly as you said. For any emergent situation, they know how to reach somebody who can help provide that support.

DR. SCHWAITZBERG: Thank you. We'll continue around the room with Dr. Afifi.

DR. AFIFI: Thank you. Abdelmonem Afifi.

I have two questions. The first is why was the final eligibility not done before randomization?

DR. HASSANEIN: Thank you, Dr. Afifi. This was a topic that we thought about extensively, and we looked at extensively during the IDE process. We wanted to have the randomization protected as much as we could. Unfortunately, due to the transplant logistical complexities, primarily the fact that we used two to three units of packed RBCs, the blood banks of all trial centers unanimously refused the notion that with this valuable resource, that potentially with a randomization, 1:1 randomization, that 50% of these blood units will be discarded.

A second issue is we worked very closely with the organ procurement organizations and the transplant team, adding the logistic step of priming and preparing the circuit at a very, very critical time of the donor retrieval process; that would have been a very, very

complex situation.

DR. AFIFI: Thank you. My second question has to do with two slides you presented. One of them is CO-68, if you could show that again. My question is, why were these blue ones for the control group not counted in the previous slide, which is CO-66 that showed 100% survival?

DR. HASSANEIN: Right. The difference between the two slides is that CO-66 reflects the 30-day mortality only. The second slide, CO-68, reflects the 30-day plus in-hospital mortality. So there's an additional time window that those patients were in the hospital, and they died after the 30 days. That's the difference in the count.

DR. AFIFI: So this happened after 30 days?

DR. HASSANEIN: That is correct.

DR. AFIFI: Okay.

DR. HASSANEIN: But within the initial hospital admission.

DR. AFIFI: Thank you.

DR. YUH: David Yuh.

Thank you very much for a nice presentation. One question. The benefits of OCS are the premises that it reduces ischemic injury, leading to lower BOS down the road. But it's my understanding that BOS is largely driven by immunologic injury mechanisms. Did you do any histocompatibility matching or analysis to make sure that they were -- the incompatibilities were equivalent between the OCS and control groups?

DR. HASSANEIN: Not as part of the study. This study was designed to really take standard lung transplantation and randomize to the preservation method.

DR. YUH: So no parameters of histocompatibility were recorded on any of these patients?

DR. HASSANEIN: Not that I'm aware of.

DR. YUH: Okay, thanks.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: Thank you very much for your presentation. I'd like to focus on the equipment for a second, the OCS console and the lung perfusion module. Have you had any failures on the consoles, and do you recommend people take one console on a transport or two consoles?

DR. HASSANEIN: We have 12 reported device malfunctions by investigators in the INSPIRE trial. Of the 12, 4 to 6 were related to one component, and it was a component in the disposables. We use a high-efficiency 20 µ filter, and at higher flow, that filter has the higher inertia. That has been fixed since May of 2013. There was one reported -- actually, two reported device malfunctions related to the hardware, one in the gas regulator. The area where the gas line is connected, it originally was made of plastic, and it was broken during use, and it has been changed to stainless steel. There's one other, a second hardware failure was related to the battery. There was a capacitor in the battery that just was one event that was reported when the battery completely discharged and the user wasn't recharging the battery. We've looked into that matter and made sure that we upgraded that capacitor, and since then, knock on wood, we have not had any hardware failures.

DR. SCHWAITZBERG: All right, let's move on.

Dr. Yusen.

DR. YUSEN: Hi. Roger Yusen from St. Louis.

I'm going to ask four questions. I have one related to randomization, and that's already been asked, but I want to clarify. Why not follow all randomized patients to assess outcomes?

DR. HASSANEIN: The definition of what we are referring to as mITT was

recommended by FDA. And can I get the definition slide, please, of the mITT population? We accepted it exactly as was defined, and as you will see the definition slide shortly, it clearly states that to be a part of the mITT population of the study, you need to be -- this is the slide -- you need to be a consented recipient that a matching and eligible donor lung has been harvested in anticipation of a transplant. Thus, any donor screen failures that did not meet that criteria, we don't have any data on them.

DR. YUSEN: Yeah, I understand what you're describing in that group, but why not follow the randomized patients in case one wants to look at an analysis of all randomized patients?

DR. HASSANEIN: I'd like to invite Chris Mullin to specifically address that question, we looked to that, and in response to some of the questions raised.

MR. MULLIN: Good morning. Chris Mullin, biostatistician with 3D Communications. I am a paid consultant to TransMedics but have no financial stake.

So, with regards to your question, in preparation for the meeting, we did do some additional analyses that weren't displayed earlier. I think if we can get it up -- and if we can't now, we'll show it later this afternoon -- some analyses to try to assess an intent to treat based on the 407 randomized. So I don't believe this analysis has been shared with FDA, but I'll display it here, as you've asked for it.

So this is based on the 407. Here, we're showing the treatment difference. Again, a negative difference favors the OCS arm over control, so you can see that was 3.1%. The lower confidence bound -- the upper confidence bound, excuse me, extends to 4.7%, so a bit above the 4% margin. For this, to get to the 407, what we did was there was some information available on nine U.S. subjects where they had known outcomes off-study, and so that was used. For the remaining patients, there was a multiple imputation model, a very simple model without adjustment for covariates; it just used treatment group, and that

was used to produce the treatment value and confidence interval.

DR. YUSEN: Thank you. My next question relates to blinding. It's my understanding that the clinical teams were not blinded to the randomized allocation, which could significantly introduce bias into patient care, which could affect outcomes, especially related to PGD and management related to that. Why was there not an attempt to blind the clinical teams?

DR. HASSANEIN: I'd like to invite Dr. Ardehali to comment from a clinical perspective, but from a trial management and implementation process, to our knowledge, the retrieval team, most of the time, are not the same clinical team that's following the patient and actually grading the PGD. But I'd like Dr. Ardehali to comment.

DR. ARDEHALI: Abbas Ardehali from UCLA.

In our experience, it's virtually impossible to blind a surgical team as well as the clinical team taking care of the patient postoperatively, not knowing what happened in the operating room. So, in our opinion, it was not practical, and it was not effective. As such, we did not do that.

DR. SCHWAITZBERG: Thank you. Do you have any more?

DR. YUSEN: Okay, the next question is were there -- my understanding is there were not pre-specified subgroup analyses. Please clarify that. And if there were not, any comments about showing multiple post hoc analyses and their meaning?

DR. HASSANEIN: Sure. I'd like to ask Chris Mullin to address that question, please.

MR. MULLIN: Chris Mullin.

So there were no pre-specified subgroup analyses in the analysis plan, and so no control for Type I error rates for the p-values. We tried to identify those clearly in our presentation, what was post hoc, but all the p-values presented would be nominal, so many of them would be considered supportive in nature on a lower level than the pre-specified

p-values.

DR. YUSEN: The last question relates to site effects and site imbalance. It's my understanding that Hannover had 26% of the patients in the study and that the FDA had suggested a 10% maximum per center and the protocol had set an enrollment cap at 20%. So if I understand correctly, why was Hannover allowed to go over 20%?

DR. HASSANEIN: The significant delays that occurred in initiation of the study in the U.S. put significant pressure on the accrual of the study and the centers that were enrolling in the study. We've communicated that we'd like to open the cap only in certain situations, and I will look specifically into that communication, and with your permission, I will bring -- I will find the exact communication pattern with FDA, if any, and I will report back after lunch break to be specific to answer that question.

DR. SCHWAITZBERG: Thank you.

Dr. Nathan, any questions?

DR. NATHAN: Yes, I do. I have four questions as well, and I'll try to run through them pretty quickly. When you talk about BOS, I think it's important to have an understanding of what BOS is. It's a 20% reduction from the patients at best baseline lung function. I didn't see anything on baseline lung function. And so you have to present that in the context of talking about BOS because the question becomes if someone attains 100% of what the predicted is for a normal person of their size and height, etc., and then they go down to 80%, that's BOS. But you can have a patient with PGD who gets to 50%, never gets above 50% at baseline and hangs around at 50% and never qualifies as BOS. And so which is a better outcome, the patient who hangs out at 50% or the patient who qualifies as BOS at 80%?

And arguably, I would say that best baseline lung function and perhaps time to best baseline lung function is a better outcome measure than BOS 2 or 3 years later when there

are so many different factors that can cause BOS, and it's difficult to attribute BOS to something that happened in the perioperative period, even though there is that association. So that's my one question and comment.

The second thing is the protocol was all in bilateral lung transplants.

DR. HASSANEIN: That's correct.

DR. NATHAN: Is there any experience with single lung transplants or taking two lungs and transplanting them into two recipients? And if the device is approved, how is that going to be managed in terms of availability for single lung transplants?

DR. HASSANEIN: Sure.

DR. SCHWAITZBERG: Let him do his two questions; otherwise, he won't keep track of all four of them.

DR. HASSANEIN: Sure. So let me address the second question. The study was for bilateral lung transplant. If we're fortunate to be recommended for approval, our indication for use is for double-lung transplant. That's the data that we have. I don't have any knowledge of single lung transplants that's been performed of the OCS, certainly not in the U.S., and I don't believe we have any outside of the U.S. So, so far it's been a double-lung transplant experience.

Related to the first question related to BOS, we completely understand the complexity that goes into diagnosis of BOS, and that's why, first of all, BOS was specified in the protocol as an additional clinical endpoint, and given the complexity of diagnosing BOS, we stipulated in the protocol that we will use the site diagnosis of BOS, given their -- they have the best information to make that final clinical decision. Our hope is that if we go to the post-approval plan and continue to collect additional BOS data, that we will work with our investigators and transplant pulmonologists to really hone in on the BOS and really take an in-depth look on the BOS, especially for collecting data out to 5 years. That's our hope.

DR. NATHAN: Do you have any baseline -- what the best baseline lung function is? That's what I'm more interested in. And if you do, perhaps that can be shown after lunch sometime.

DR. HASSANEIN: I will look into that, and I will report back after lunch break.

DR. NATHAN: Then, another point: You talk about ischemic time, and I think the total cross-clamp time is a much more important and relevant measure than ischemic time because we don't know when the patient -- when the lungs are being perfused, if that's truly, you know, what's the difference between cold ischemia and warm ischemia. So I think the value of the system is increasing the time that the lung is out of the body and the logistical advantages associated with that. What I would also like to see are maybe subgroup analyses of those patients who had the longest cross-clamp time --

DR. HASSANEIN: Sure.

DR. NATHAN: -- to see what the outcomes are, rather than ischemic time.

DR. HASSANEIN: Sure. Can I get, please, the slide with the cross-clamp time quartiles, please? The first one and the second one, please. This is a slide that the FDA had asked us to perform a post hoc analysis, looking specifically at cross-clamp time for first and second lung, identifying the first lung less than 300 minutes/greater than 300 minutes, and second lung less than 400 minutes and greater than 400 minutes. And as you can see here, the blue column is control, the red column is the OCS arm, and the pink column is the OCS solution subgroup. So, as you can see, in all time, cross-clamp time windows specified in this post hoc analysis, the OCS seems to perform better than control at all the four time points for both first and second lung.

DR. NATHAN: Thank you.

DR. SCHWAITZBERG: Dr. Meyer. We're going to move on.

DR. NATHAN: Okay.

DR. SCHWAITZBERG: We'll get it in deliberations.

DR. MEYER: Dan Meyer.

I have three quick questions. The first one relates to study design. The number of screening failures has come up in both groups, and with the 43 in the OCS group, higher than what would be expected in the -- you know, from the UNOS data. Does this introduce any bias when your statisticians have to assess this?

DR. HASSANEIN: Sure. I'd like to invite Dr. Ardehali to address that question.

DR. ARDEHALI: Abbas Ardehali, UCLA.

We agree with you, there is an imbalance in terms of the screen failures between the two arms. We have studied this thoroughly, right and left, upside down, to try to find out if there's an explanation for this. We could not find any. But to reassure about the validity of the data, I think this slide provides some confidence, which is to say that the quality of the donor lungs that were transplanted in both arms was nearly identical. There may have been some bias, some favoring of one of the arms, but at the end of the day it was not favoring OCS. The quality of the donor lungs that were transplanted were nearly identical.

DR. SCHWAITZBERG: We'll catch it in deliberations.

Do you have any more questions that you wanted --

DR. MEYER: Can I ask one other question?

DR. SCHWAITZBERG: Sure.

DR. MEYER: Related to the other pretty significant difference, at least early on, would be again safety of the device and the surgical issues, surgical and cardiac issues related to that. Instead of increasing your number of sites, that if you would get approval, you'd look at the increased number of sites, would this data -- the safety -- which is dramatic in terms of the number of deaths early on, would this cause you to actually

decrease the number of sites that you'd address, make this technology available to -- because your higher enrolling centers, Hannover and UCLA, you know, I don't know if they had a significant number of these patients, but I would think not. So would this data here -- because it does seem that there is a significant technical component to your outcomes.

DR. HASSANEIN: I want to clarify one point, that we definitely acknowledge and we're very, very concerned at the 30-day mortality. However, when you look at the detail of the cardiac and vascular mortality, you will find -- I hope you will find very quickly these are iatrogenic surgical, and a patient overdosed on Coumadin, an INR of 5.6, stroked at home. You know, a transection of the LV during VAT-assisted -- however, to address your specific question, our plan for rollout is a controlled rollout in the United States. We are going to target for the first year the trial sites, and we are going to work with the trial sites first and roll that out slowly for the second year only up to another 20 centers maximum, so to ensure that we're maintaining high-quality outcomes. That's our goal, that has always been our goal, and we were absolutely focused on that 30-day mortality ourselves.

DR. SCHWAITZBERG: Dr. Moon.

DR. MOON: Marc Moon.

A three-part question, and I'm going to ask it all at once. Was there a difference between prophylactic ECMO between the two groups? How many Grade 3 PGDs were because of ECMO in each of the groups? Just ECMO alone, not the other criteria. And was there a difference in use of nitric oxide between the groups?

DR. HASSANEIN: Sure. Let me address it from the bottom up. There was no difference in the use of nitric oxide between both groups. There was eight protocol ECMO on the OCS and five on the control. We performed an analysis in two different ways. We censored those ECMOs similar to the *New England Journal of Medicine* publication where they were censored out, and we've also included them as a sensitivity analysis as PGD3. It

doesn't change the conclusion of the primary effectiveness endpoint. It did not have an impact. And I don't have the exact number of PGD3's that were graded with ECMO. If you allow me to get that specific number after lunch?

DR. SCHWAITZBERG: Terrific. I have five questions but will only ask one.

(Laughter.)

DR. SCHWAITZBERG: And I let the discussion go on a little bit longer so people could ask questions about training. Since the FDA is not making a device, those questions won't exist. So I want to ask a process question.

DR. HASSANEIN: Yes, sir.

DR. SCHWAITZBERG: Having been on a DSMB, having been an IRB chair, having organized a trial that had a DSMB, the medical monitor is an employee of the company; is that not true?

DR. HASSANEIN: That is not true.

DR. SCHWAITZBERG: So how is the medical monitor compensated?

DR. HASSANEIN: The medical monitor is compensated through standard consulting agreement honorarium that's similar to any traditional trial management.

DR. SCHWAITZBERG: So he's a contract employee of the company?

DR. HASSANEIN: He's a consultant to the company, yes.

DR. SCHWAITZBERG: A consultant to the company.

DR. HASSANEIN: Yes.

DR. SCHWAITZBERG: So while the monitor is impeccable in his qualifications, there is no doubt, is it -- I thought it was unusual that the medical monitor, who is a consultant to the company, is sitting on the DSMB and made a statement that his role in the DSMB didn't have any impact on why the protocol changes were initiated after the DSMB. So what I'd like is some clarification on his role in the DSMB. Was information from the DSMB brought

back to the company, which then potentially said, hey, we need to change our endpoint? So could you clarify this? This went by pretty quickly, so I'd like clarification on this.

DR. HASSANEIN: Sure. I'd like to provide clarification, but also I would like to invite both Professor Wallwork and Dr. Josh Sonett, who is the chairman of the DSMB, to comment from their perspectives as well.

DR. SCHWAITZBERG: Sure.

DR. HASSANEIN: From the company's perspective, and this has been communicated throughout our PMA, the medical monitor reviewed event-level data in a blinded and -- in a blinded fashion, event-level data. He didn't look at aggregate subject data. It was event-level data. The data went to the DSMB after the blinded adjudication was completed. His role in the DSMB was not as the chair; the chair was Dr. Sonett. So that's just a clarification from the company's perspective, but I'd like to invite Professor Wallwork and Dr. Sonett to clarify, if you have any additional clarification.

DR. WALLWORK: Yes, I have. John Wallwork.

I actually didn't start adjudicating any of the data until after the protocol changes, so I had nothing to do with the protocol changes.

DR. SCHWAITZBERG: We can't hear you. If you could just speak up.

DR. WALLWORK: Sorry. I had nothing to do with the protocol changes because -- and I didn't, indeed, look at any of the adjudications until after the protocol changes had happened. So I had no way of influencing those at all.

DR. SCHWAITZBERG: So, in terms of safety and efficacy, how does the DSMB make a decision if they don't have an awareness of how you adjudicated the data, since you just said it wasn't adjudicated? How do you make --

DR. WALLWORK: No, no.

DR. SCHWAITZBERG: How do you make a safety discrimination at the DSMB level?

DR. WALLWORK: Sorry, sorry. I think you missed my point. The data that went through the DSMB had been adjudicated, but I did not adjudicate any data before, prior to the protocol change. So I had no way of being involved in or discussing or affecting any of the protocol changes. I did not do any data adjudication until after that had happened and the data that went to the DSMB had all been adjudicated.

DR. SONETT: Josh Sonett, Columbia University, DSMB chair.

In terms of protocol changes, there was no communication from the DSMB to TransMedics regarding safety concerns that we thought maybe warranted changes in anything because the stopping rules and the SAEs were, we thought, reviewed independently and not felt to be a part of the device.

DR. SCHWAITZBERG: So there were no outcomes data that were communicated?

DR. SONETT: Correct, in a reverse way. We only asked for information; we never gave information.

DR. SCHWAITZBERG: Thank you. I'm going to take one question. Then we'll go to the break.

DR. CONNOR: Yeah, I was going to say it was unblinded, though, for the Sponsor, right? So even the DSMB didn't communicate data. I thought the Sponsor actually had access to the data throughout, as data accrued.

DR. SCHWAITZBERG: Yeah, I just wanted to make that point. All right, it is --

DR. FISHER: Dr. Schwaitzberg, can FDA have the privilege of a quick question?

DR. SCHWAITZBERG: You do. You're Dr. Fisher; you do.

(Laughter.)

DR. FISHER: Thank you for recognizing me.

Dr. Mullin, first. I think you are correct in that your analysis hadn't been shared with FDA, but I appreciate you acknowledging that up front.

I think my question, my first question, is very close to Dr. Yusen's and just a point of clarification. For the logistical failures, for the ones that were randomized to OCS, if there was a logistical failure, they went on to go for standard of care cold storage?

DR. HASSANEIN: Right.

DR. FISHER: And those lungs were transplanted?

DR. HASSANEIN: Yes.

DR. FISHER: On or off study?

DR. HASSANEIN: They were transplanted off study.

DR. FISHER: So data status on that? We don't have any data, correct?

DR. HASSANEIN: Can I get the slide up? Of the 10 logistical screen failures, 2 were related to device malfunction prior to going out to retrieve the organ, so they were transplanted on ice, off study. Those two patients we have data on; they survived, and I can look further on any additional data. The rest were all transplanted off study, and we have no additional data on those subjects.

DR. FISHER: Okay, thank you. And the last question. The endpoint was actually 30-day survival. You took that past 30 days, and you included something called in-hospital time. Do you have any details as to -- maybe after lunch you could provide some additional information. Do you know how long that period ran, and was it similar between the two groups?

DR. HASSANEIN: Sure. The definition of in-hospital mortality, Dr. Fisher, was focused primarily on patients that did not leave the initial hospital for transplantation, regardless of the time. These patients were intubated, they were in ICU, and they died within that initial hospital. I will get the specific days, number of days, and make sure that we look at them after lunch, if it's okay with you.

DR. FISHER: Great, thank you.

DR. HASSANEIN: Thank you.

DR. SCHWAITZBERG: All right, it is 10:28. We will take a 10-minute break. I'd ask the Panel members to get in their seats at 10:38, reminding that you may not discuss the trial with other Panel members or with anybody in the audience.

(Off the record at 10:28 a.m.)

(On the record at 10:40 a.m.)

DR. SCHWAITZBERG: All right, good morning. If everybody would take their seats so we can get going. It is now 10:40. I would like to call the meeting back to order. Next, the FDA will make their presentation.

I would like to remind the public observers at this meeting that while it's open to the public for observation, public attendees may not participate except at the specific request of the Panel Chair.

The FDA will also have 90 minutes, and when we ask clarifying questions before the lunch, I would ask the panelists to be very specific and ask questions for clarity, and we will get into the discussion topics for deliberation after the session. If the FDA would now begin their presentation.

DR. FARIS: My name is Owen Faris, and I'm the Director of the Clinical Trials Program in CDRH's Office of Device Evaluation. And before we get into the scientific presentation from FDA's review team, I'd like to just spend a few minutes walking through some of the regulatory aspects of how we render decisions for IDEs.

So just very briefly, I'm going to talk about what is an IDE, what are our decisions for IDEs, some changes in the law that happened a few years ago that impact today's discussion, and how we communicate other information separate from our decision for IDEs.

So, first, an Investigational Device Exemption, or IDE, is the process by which FDA

grants approval for U.S. human study of significant-risk devices which are not approved or cleared for the indication being studied.

And very briefly, this is the process by which we review those decisions. So a sponsor submits an IDE application to FDA. FDA constructs a review team to review that application, and within 30 days we render a decision, and that's for original questions about starting a study, and that's also for changes to studies that are already under way. And if approved, the sponsor seeks IRB approval, and after both FDA and IRB have approved the investigation, the study may begin.

So when we render a decision, whether it's for a new study or for changes to an existing study, we convey one of three decisions: either we grant full approval to that request, which means we don't have any additional questions, and upon IRB approval, the sponsor may begin that study or make that change; or we approve the study with conditions, which again means that the study may start upon IRB approval, but FDA has some additional questions that must be answered within 45 days; or alternatively, we disapprove the study because we have concerns that need to be addressed before that study is begun or before that change is initiated, and the sponsor cannot begin that study until they respond to FDA's concerns and either get approval or approval with conditions.

So back in 2012 some changes were made to the law that impact today's discussion, and specifically, I'm going to read some changes to the FD&C Act, and it states that "FDA shall not disapprove an IDE because:

- the investigation may not support a substantial equivalence or de novo classification determination or approval of a device;
- the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or
- an additional or different investigation may be necessary to support

clearance or approval of the device."

And so translated to simpler language, this means that FDA cannot be -- that an IDE cannot be disapproved on the basis of FDA's belief that the study design is inadequate to support a future PMA, 510(k), HDE, or de novo classification.

So a few points about that: The standards for protecting study subjects remain unchanged. If we have concerns around the study subjects, human subject protection issues that should preclude starting of that study, we will disapprove that study.

The standards for market approval remain unchanged. So today we're here to discuss a marketing approval application, and you should consider whether the study design was appropriate in that rendering.

And issues regarding study design that are related to protecting study subjects may still be the basis for disapproval or approval with conditions.

So how do we convey elements of our review that don't relate to whether we're going to approve or disapprove the study? FDA still conducts a complete scientific review of an IDE application, so we make a determination as to whether the study should be approved based primarily on human subject protection issues. But we also assess the adequacy of the study design to meet its study goals, and we develop something called study design considerations, which are conveyed in FDA's letter to articulate elements of the study that we think should be considered for change based on our review.

So these are recommendations to a sponsor regarding changes that FDA believes should be made in order for the study to support its primary goals. And these are examples of the kinds of things that are conveyed in FDA's decision letters, not generally the basis for disapproving the study but conveyed as things that we think the sponsor should address to support the study to meet its goals, issues such as:

- Issues that may bias the study results;

- Primary and major secondary endpoint issues;
- Randomization, control, and blinding;
- Follow-up duration and assessments; and
- Statistical analysis plan.

So just a couple of slides in summary: If we grant approval or approval with conditions, the study can start right away. If we have approval with conditions or disapproval, that means we have questions that need to be addressed by the sponsor. But study design considerations do not require a response from the sponsor. They can consider them, and we hope they consider them. If they wish to make changes to the study, they need to submit an IDE supplement, and we will consider those changes, but they don't have to. And these issues are all conveyed in a guidance document focused on FDA decisions for IDEs.

So when we turn to the marketing application, which is what we're here to discuss today, a sponsor may or may not have modified their study to address our study design considerations. And upon review of the study data in the marketing application, we may raise those study design considerations to a future panel discussion, such as we're here to discuss today, and hopefully that will help support the discussion that goes forward.

And now I'm going to turn the projector over to Andrew Fu, who will begin the scientific presentation.

DR. FU: Good morning, my name is Andrew Fu. I am the lead reviewer for TransMedics' premarket approval application for the OCS Lung System. On behalf of the review team, we would like to thank everybody for being here this morning.

I would like to acknowledge my team for all the hard work they've put in in the past year, some of whom you will be hearing from later this morning.

I will start FDA's presentation this morning with a background on the OCS system, its

associated nonclinical testing as well as a brief history behind the INSPIRE trial. Next, my colleagues will present the clinical and statistical considerations of the INSPIRE trial. We will end our presentation with recommendations on the proposed post-approval study.

As a recap, the TransMedics OCS system is a portable organ perfusion, ventilation, and monitoring medical device intended to preserve donor lungs in a near physiologic, ventilated, and perfused state for transplantation.

The OCS Lung System consists of three main components. First, the lung console: It's a portable enclosure that houses the non-sterile and reusable components of the OCS system, including its electronics and software that are responsible for controlling the ventilation and perfusion functions. In addition, it includes a wireless monitor that displays and controls the lung preservation parameters.

Next, the lung perfusion module: It includes a reservoir that houses the donor lungs as well as other sterile and disposable components that complete the perfusion and ventilation circuit.

And, finally, the OCS lung solution, its proprietary sterile solution that is chemically equivalent to Perfadex, and during use, it is mixed with packed red blood cells and other additives and pumped through the donor lungs.

TransMedics performed nonclinical testing on the OCS Lung System as a whole, including engineering and bench, electrical safety/electrical magnetic compatibility, software verification and validation, and a few animal studies for the purpose of validating design changes.

In addition, TransMedics performed biocompatibility, sterility, and shelf-life testing on the disposable components of the OCS system. FDA reviewed the test results and determined that they're acceptable.

Next, I will switch gears and present a brief regulatory history of the INSPIRE trial.

The study was originally designed to enroll 320 subjects, with the first subject transplanted in November 2011. The study was originally approved to use only Perfadex solution. In October 2012, FDA approved TransMedics' request to use OCS lung solution as an alternative to Perfadex after TransMedics submitted testing to show that the two solutions were chemically equivalent.

One year later, in December 2013, TransMedics changed the primary endpoint and the primary analysis population of the INSPIRE trial. FDA strongly advised against this change, given that at the time 71% of the original 320 subjects had already been transplanted.

Fast forward towards near the end of the study in July 2014, after an unplanned interim analysis showing that subjects who were treated with the OCS solution were performing better than subjects who were treated with Perfadex, TransMedics apprised FDA of their decision to pursue marketing application of the OCS system with only OCS solution.

Subsequently, TransMedics planned for a study expansion in order to address concerns of lack of statistical power of the OCS solution cohort. However, at this time, the trial was facing enrollment stop. In August 2014, FDA approved TransMedics' request for an additional 29 subjects, later to be referred to as the administrative extension cohort, in order to avoid this enrollment stop. TransMedics retracted plans for the definitive study expansion after they uncovered sample size calculation errors. In contrast, all 29 subjects from the administrative extension cohort were fully implemented, with the last subject transplanted in November 2014.

I would like to end with three takeaways. First, the INSPIRE study design and analysis plan underwent significant changes during the study. The circumstances under which these changes were made as well as the implications will be discussed in more detail

by my colleagues.

Two, the 29 subjects from the administrative extension cohort represented an approximately 10% increase from the original 320 subjects. In addition, these subjects were treated using the same clinical protocol. Therefore, FDA considers the original 320 subjects plus the 29 subjects from the administrative extension cohort, totaling 349 subjects, to be the definitive INSPIRE population.

And, finally, the OCS solution is chemically equivalent to Perfadex. Therefore, FDA considers all OCS lung solution subgroup analyses to be adjunctive.

And with that, I would like to introduce Ms. Sherry Liu to present FDA's statistical considerations.

MS. LIU: Thank you, Andrew.

Good morning, my name is Sherry Liu, and I am a statistical reviewer for this submission. Today I will be going over the INSPIRE study design and some of the statistical concerns present in this study.

This is the outline of my presentation. I will briefly go over the study design and highlight some of the important issues with this study's effectiveness endpoint, analysis populations, and patient disposition. I will conclude with some statistical concerns that need to be taken into consideration when reviewing the results of the INSPIRE study.

The TransMedics Organ Care System was studied in a prospective, randomized, controlled, international, multicenter clinical trial. In this trial, the OCS Lung System was compared to the cold storage standard of care for preservation and transportation of donor lungs using a non-inferiority hypothesis, meaning the Sponsor only had to show their device was not clinically inferior compared to the standard of care.

INSPIRE is an unblinded study with a total of 320 subjects planned to be enrolled across 21 centers in the U.S., Europe, Australia, and Canada. There were no planned

interim analyses, nor were there any adaptive design features pre-specified in the protocol.

As indicated earlier, there was an originally approved primary endpoint which was agreed upon by both the FDA and the Sponsor at the start of the study. This endpoint was a composite of survival at Day 30 post-transplantation and absence of ISHLT primary graft dysfunction, also referred to as PGD, Grade 3 at 72 hours post-transplantation.

However, after a majority of the study's subjects had been enrolled, the primary endpoint was modified to evaluate PGD3 within 72 hours instead of at 72 hours post-transplantation. This change allowed for the inclusion of PGD grading at time points 0, 24, 48, and 72 hours post-transplantation. FDA had expressed disagreement for changing the primary endpoint in the middle of the study with a study design consideration to the Sponsor.

As good practice of clinical trial design, the primary endpoints and hypotheses should be pre-specified before a trial begins. Modification to a primary endpoint in the middle of the trial may introduce bias or even compromise the scientific integrity of a trial.

Therefore, FDA had the following concerns:

- This study was an unblinded trial.
- The decision to change the primary endpoint was done when more than two-thirds of the initial cohort had been transplanted.
- The primary endpoint results on a majority of the subjects were already available. Therefore, FDA is concerned with the possibility that the change to the primary endpoint was made based on the knowledge of outcome data.

The hypothesis for the primary endpoint is that the OCS treatment is non-inferior to the standard of care, with a non-inferiority margin of 4%. This is exactly the same for both the initial primary endpoint and the modified primary endpoint. The non-inferiority bound remained the same, despite the change in endpoint. The Sponsor also pre-specified that if

non-inferiority was demonstrated, a corresponding test for superiority would be performed.

If non-inferiority was established for the primary endpoint, then there were three secondary endpoints pre-specified. To preserve the Type I error rate, a fixed sequence testing procedure was used, shown in the order as follows:

The first secondary endpoint to be examined was incidence of ISHLT PGD Grade 3 at 72 hours post-transplantation with a non-inferiority margin of 5%. This endpoint represented the PGD component of the initially agreed-upon primary effectiveness endpoint.

The next secondary endpoint examined was the incidence of the ISHLT PGD Grade 2 or 3 at 72 hours post-transplantation with a non-inferiority margin of 7.5%.

The third secondary endpoint was the overall survival at 30 days post-transplantation with a non-inferiority margin of 4%. This endpoint represented the mortality component of the primary effectiveness endpoint. This all-cause mortality endpoint was the only pre-specified endpoint to assess mortality.

Per the ICH E9 Statistical Principles for Clinical Trials, the intent-to-treat, or ITT, population is the preferred analysis population. Preservation of the initial randomization in analysis is important in preventing bias and providing a secure foundation for statistical testing. Post-randomization exclusions will undermine the comparability of study arms produced by randomization. Inferences based on arbitrary or ad hoc subgroups of subjects in the trial is challenging to interpret and generalize.

Now I will introduce the analysis populations defined in the protocol. Although the ITT is the ideal analysis population, we always do consider all of the data and populations defined in a given study. Due to the nature of organ transplants and the logistic limitations of this study, the closest we can achieve is a modified ITT analysis population. The modified ITT analysis population was originally set as the primary analysis population in the protocol.

The modified ITT population, as defined in the protocol, consisted of all randomized subjects for whom a matching lung has been harvested and determined to be eligible for preservation with either control or OCS before any attempt has been made to preserve the lung with either control or OCS. By this definition, screen failures should only be subjects where there hasn't been any attempt to preserve the lung. Later in the presentation, Dr. Sapirstein will explain how some of the screen failures were wrongly categorized based on this definition.

The per-protocol population consisted of all randomized patients who were transplanted and have no major protocol violations and for whom the eligible donor lung received the complete preservation procedure as per the randomization assignment.

The Sponsor changed the primary analysis population from the modified ITT to be the per-protocol population after 71% of subjects had already been transplanted. We have expressed our concerns pertaining to this change in a study design consideration to the Sponsor. Dr. Sapirstein will elaborate in his presentation on how per-protocol population was derived.

So now that we have all of the major effectiveness analysis populations defined, let's take a look at the patient disposition diagram for this study. I hope to give you an overall picture of the analysis cohort before diving into the details of the major analysis populations.

The green boxes indicate each of the analysis populations that were used in performing data analysis. These cohorts include the ITT population, INSPIRE cohort mITT, combined cohort mITT, combined cohort PP, and INSPIRE cohort PP. Due to limited information on the screen-failed subjects, the ITT population could not be fully constructed. This population was only used in the sensitivity analyses.

On the left-hand side, marked by red, represents the OCS treatment arm. Here I

separated out the administrative cohort and the initial cohort. As you recall from Dr. Fu's presentation, an administrative cohort was added after the initial cohort had finished enrolling. The administrative cohort was simply an extension of the initial cohort, so the patient population was essentially the same. FDA used the combined cohort rather than only concentrate on the initial INSPIRE cohort for all major analyses.

The right-hand side, marked by blue, represents the control arm. The boxes with yellow dashed lines on each side indicates where the subjects were taken out of the patient population. For example, there were 6 and 37 subjects taken out of the OCS treatment arm and treated as screen failures, whereas there were only 2 and 13 subjects taken out of the control arm and treated as screen failures.

If you have noticed a stark imbalance in the screen failures, you are correct. There seems to be almost three times more screen failures in the treatment arm compared to the control arm. This imbalance is also seen in the protocol violations.

Do not try to absorb all of this diagram in. I will step through each of the analysis populations and its composition in more detail in the next few slides, but this is to give you a sense of the complexity of the analysis populations in this study.

Let's start with the ITT population, which is composed of all subjects randomized. Due to logistic limitations in this study, randomization needed to occur before some inclusion and exclusion criteria were checked. Therefore, there were some subjects that were taken out of the study and treated as screen failures even after randomization.

Since screen failures should be declared before any attempt is made at preservation, you would expect it to be relatively balanced between the two treatment arms. But as we saw in the previous diagram, there is a great imbalance of screen failures that is observed between the two treatment arms.

In fact, we see almost a three times factor between the two treatment arms. Given

this is an unblinded trial, this magnitude of imbalance of screen failures statistically makes one suspect there might be potential selection bias present in the removal of subjects as screen failures. Dr. Sapirstein will present some supporting information that were found during review in relation to this issue.

This flow diagram shows how the mITT population is further reduced to the per-protocol population. Again, we see more than two times major protocol violations in the treatment arm compared to the control, raising concerns about possible selection bias in picking out the per-protocol violations in the two treatment arms. Dr. Sapirstein will again present some supporting information in his presentation as to the inconsistencies of identifying major protocol violations between the two treatment arms.

So this ends my discussion on analysis population.

In summary, as you can see, there are many statistical issues present in this trial. The disproportionate screen failures from the two treatment arms jeopardizes the property of randomization and introduces potential selection bias into TransMedics' safety and effectiveness analyses.

Due to the missing data created by the screen failures, it is difficult to quantify the magnitude of the bias, therefore making it a challenge to interpret the study results.

Unbalanced major protocol violations may have caused selection bias in the per-protocol analyses. Therefore, it should not be considered to be the primary analysis population.

Furthermore, the unplanned interim look at the data and major changes to the protocol, such as the primary endpoint definition and the primary analysis population, may imperil the study integrity. These are just a few of the major concerns.

To conclude, due to all of these issues I have mentioned, the validity of the trial may have been compromised. Therefore, it is a challenge to interpret the study results both in

the mITT and per-protocol population. Please take these points into your consideration when you consider the overall results reported in this study.

This concludes my presentation. Thank you.

Now I would like to introduce the next presenter, Dr. Sapirstein, to go over the clinical portion of the presentation.

DR. SAPIRSTEIN: Hi, good morning. My name is John Sapirstein, and I am a cardiothoracic surgeon in the Office of Device Evaluation, and I'm going to review some of the clinical details that we uncovered during our review of this PMA from TransMedics.

So I'll talk a little bit about the background of the trial design, and you've heard a lot about it already. I'll give a brief overview from our perspective on the IDE protocol that was used and the trial execution, and I'm going to highlight some of the limitations that we identified during the PMA review. And as you've already heard from Ms. Liu, one of those limitations, we feel, is a potential for selection bias that is important to consider. We'll go over the primary effectiveness endpoint results, and I've got that pluralized there because, as you've heard already, there are actually two primary endpoints that we're considering now. And I'll talk about some of the key secondary effectiveness endpoints and adjunctive analyses that we think are critical to the consideration of the device.

So this is a background, if you will, of the IDE study for INSPIRE. You can see it was submitted in 2010. The rationale for proceeding with the trial has already been talked about; a significant number of patients die on the transplant waiting list, and conversely, many donor lungs that perhaps could be used are not harvested. There are known limitations that the Sponsor has clearly outlined for the cold static preservation, and also, as the Sponsor indicated, the use of the device has the potential for allowing monitoring of the harvested lungs.

So the premise of the OCS lung device is fairly straightforward; it is presumed that it

will minimize the organ damage and that that should lead to better allograft function after the transplantation. And the hope, then, is that down the pike, that better allograft function will also translate into optimized recipient survival. And secondarily, as the Sponsor also indicated, there's a suggestion that use of the device will allow flexibility to the entire organ harvest construct.

So, as Dr. Fu mentioned, FDA found acceptable the preclinical as well as some of the initial, outside U.S. clinical early feasibility investigations, and our approval of the IDE was in no small part related to the fact that FDA had substantial familiarity with other clinical trials from the Sponsor using the OCS platform.

So the primary objective, as you've seen this already, was to compare the safety and effectiveness of the OCS device to standard of care, which would be cold static storage, and I've highlighted -- underlined "compare" because, as was mentioned already, the trial was not designed to either show superiority clinically or statistically.

The proposed indications for use you've seen as well. I'll just point out that the indications for use is talking about donor lungs, and there is no distinction between the so-called standard criteria lungs and expanded criteria donor lungs in the proposed indications for use.

So this is the design, and you've heard this many times; it was 1:1 randomization in U.S. and non-U.S. sites, and randomization occurred at the time of enrollment. Enrollment was at the time of consent signing. It was unblinded, which meant the randomization arm was known prior to beginning any organ harvest. There were, as was just mentioned, no interim analyses or adaptive design in the protocol. And, again, randomization took place before final eligibility about the donor lungs or the recipient.

And FDA was agreeable to this for the complexity of this trial and the fact that we realize that it's necessary to be able to have a well-conducted trial actually be put into

effect. A perfect trial, as was discussed already, might have had randomization occurring at the time of the final organ harvest, but that was not practical, and we recognize that. That said, we did this knowing that the possibility of selection bias was prevalent, and we took great pains to try to minimize that in our negotiations with the Sponsor.

So here is one of the conditional approvals shortly after the IDE was submitted, this was in 2011, and you can see that we suggested that selection treatment bias might be introduced if the per-protocol population and as-treated protocol populations were the primary analysis cohorts. So we suggested using intention to treat as the primary analysis.

Again, in 2012, we further specified what we felt was an appropriate intention-to-treat population, and it was subjects where the donor lung was harvested and it was determined that the donor lung was suitable to transplant. That was our expectation for an intent-to-treat population.

And the Sponsor shortly thereafter agreed to this in 2012, and this led to the final approval of the study in March of 2012. Again, intention to treat, defined there, was the main analysis population. Per protocol would be a standard per-protocol population of randomized subjects who have no major protocol violations.

Now, not to belabor the point, but I guess I will belabor it a little bit, what do we mean by -- what were our expectations for subjects for whom a matching lung had been harvested? Well, again, we wanted to be reasonable to account for unexecuted harvests. We know full well, if you go on a harvest, perhaps a donor lung wouldn't be taken, perhaps the patient on that given day was not an appropriate recipient, so we didn't want that patient-donor match to be part of the intent-to-treat population. So, as you can see, these are the criteria, if you will, that we thought were reasonable reasons not to be included in the intention-to-treat analysis.

In terms of what we meant by eligible for preservation with the two arms of the

study, standard of care or the device, we felt that this should be essentially a purely clinical characterization that the concept, as being discussed this morning, of logistic failures really shouldn't be part of the removal of patients from the intention to treat because if a lung were harvested, that suggests that the lung is eligible for preservation with either one arm or the other in a randomized study.

So intention to treat was most relevant in our opinion. We felt it balanced the rigors of an appropriate trial design with the practicality of actually allowing the Sponsor and the investigators to execute the study. And we also felt it did as much as could be possible to preserve equipoise given that randomization was known well before the time the donor and recipient evaluation was completed.

So as was mentioned just recently by Ms. Liu, the ITT population, which was being discussed during the IDE process, is really a modified intention-to-treat population. And I'll perhaps use those terms interchangeably here.

So one more issue of what would a screen failure be, just to further put boundaries on what was going to be the analysis population. This is what was in one of the previous versions of the approved protocol, and it subsequently was not in the final protocol version, but you can see that if a patient did not have treatment within the context of the investigation, and you can see the listing of what treatment would be, then that would be a screen failure.

So when we interpret this, we view treatment as meaning harvesting; the harvest process was the treatment involved in this study. If one accepts that, in our opinion, crossover to another treatment arm from, say, the OCS device to a standard of care was not a screening failure.

Likewise, off-study/off-investigational use of the device outside the United States, commercial use of the device of a randomized and enrolled patient would not be a

screening failure. They may be protocol violations, they may be protocol deviations, but they would not, in our opinion, be something that would remove a patient from the modified intent-to-treat population.

Now, I mentioned protocol violations. We fully understood that the device is more complicated than the standard of care control arm, and so we expected more protocol deviations, but we didn't expect that major protocol violations would be substantially different between the two. And that's important because we didn't think that the designation of a major protocol violation should somehow have a substantial effect on interpretability of the data.

So here are the metrics for the evaluation of effectiveness, and you've seen these already. The first one was 30-day post-transplantation survival, and this is a standard benchmark, as I'm sure everyone on the Panel knows, for a surgical procedure. It's easily captured, it really requires no adjudication, and it's a binary event, and it is clinically relevant.

Now, the Sponsor has rightly and appropriately mentioned the survival until hospital discharge, survival until hospital discharge with or without 30-day survival. We have no disagreement; these are relevant clinical parameters, but we don't think that they supersede a pre-specified 30-day mortality endpoint for this trial.

The second aspect of effectiveness was the incidence of primary graft dysfunction in the perioperative period. These, as you've heard, were based on the 2005 ISHLT consensus statement. You can see listed there are the specific criteria involved. Again, these are something that presumably were easily captured, ideally would not require explicit adjudication, and it's generally felt in the transplantation community -- and I don't think there's any argument -- that this is a relevant clinical predictor of overall function and survival of the patient post-transplantation.

This is the actual study from -- that was published by the ISHLT. You can see on the left the oxygenation and INSPIRE oxygen ratios, the radiographic aspects, and then these are the caveats, the supplemental asterisks, if you will, for the ISHLT scheme: clear x-ray, amount of oxygenation and ventilatory support, and the use of extracorporeal membrane oxygenation (ECMO). We'll be talking about it a little bit more later.

So these are the two endpoints, the primary effectiveness endpoints. They revolve around the composite of patient survival at Day 30 and the ISHLT Grade 3 findings. It was, as you've heard, non-inferiority. The non-inferior margin was 4%, agreed upon, and the two endpoints were the first one, which was pre-specified, grading primary graft dysfunction at Time 72. And I'll refer to this, as you can see, as the endpoint sub at 72. And the second one, which was the modified primary endpoint, including all four of the potential time points for measuring primary graft dysfunction.

The secondary endpoints you've heard about several times now, hierarchical in nature. And there were other effectiveness measures. Some were pre-specified without statistical testing in the protocol, and you can see those listed there, and there were other purely adjunctive analyses that were not at all pre-specified. And I've highlighted the ones that we think are particularly relevant, again, not endpoints per se in the protocol: long-term survival, bronchiolitis obliterans syndrome, and then the lung preservation times.

The safety endpoint, Dr. Bahadori will be talking about this a little bit later, but you can see it was a frequency of lung-related adverse events, and it, too, had a non-inferiority margin associated with it, and it was adjudicated by the medical monitor, as you've heard already.

The inclusion and exclusion criteria, you've seen these. This is from the recipient side. We agree, completely standard type of criteria for a trial like this.

In terms of a donor, these are the inclusion and exclusion criteria. Again, they seem

rather acceptable and appropriate for the trial, but I will just point out a couple things. What was not defined in the protocol, especially considering this is a multi-study, multinational open-label study, at time of final acceptance that wasn't specified in the trial: What exactly was active primary pulmonary disease? Not specified. What constituted moderate to severe traumatic lung injury? And what really were the criteria, hard and fast, for active pneumonia? And we'll be talking about some of these a little bit later.

Here is the enrollment in the study. As you've heard, 407 patients were enrolled, and that was the same as being randomized. This occurred between 2011 and 2014. There were 21 sites. The majority of them were from outside the United States, and the outside of the United States sites enrolled roughly two-thirds of the overall subjects.

As was discussed previously, there was in the protocol a per-site cap of 20%, but the highest enrolling site did enroll close to one-quarter of the study patients.

If one were to go from that first double column, from randomized enrolled to mITT, that is the difference in screen failures, 14% of the screen failures -- 14% of enrolled patients were screen failures, and nearly three-quarters of those occurred outside the United States. And then, as one goes from the mITT to the per-protocol, you can see an additional 14 protocol violations, again, the majority from outside the United States.

This, then, is the CONSORT diagram of that in the different populations. Here you can see 43 subjects versus 15 subjects, screen failures. There was one device failure that led to non-use of the lung. And what struck us, as we've talked about several times already, is this disparate amount and disparate ratios of screen failures, not what we were expecting in a trial like this.

When one breaks these down, we can see the donor screen failures, the recipient screen failures, and then the logistic screen failures. As I mentioned previously, the logistic screen failures was not something we were expecting to have an impact on the analysis

populations.

Just briefly, I mentioned the U.S. versus OUS. You can see that, again, more of the -- in the middle are the OUS, on the outside are the U.S. More screen failures and protocol violations in the outside U.S. study sites. And, again, the frequency of these events within the U.S. versus outside U.S. was higher.

Now, in terms of the recipient demographics, we agree with the Sponsor; they were very clinically similar overall. The lung allocation scores were similar, and I've highlighted those here in both arms. It's important to note, though, that about a third of the patients did not have lung allocation scores, again probably reflecting the international nature of the study.

Pulmonary arterial hypertension, as the Sponsor mentioned, was higher in the OCS treatment arm, and we agree with that. However, it's also important to note that the overall prevalence of this as an indication for lung transplantation was fairly low in the study. And the standard of care arm did have proportionately fewer recipients in it.

In terms of the donor organ, we agree they were somewhat similar. The standard of care arm had slightly, although probably not clinically important, lower $PaO_2$ to $FiO_2$ ratios prior to harvesting. And the gender ratios were similar in balance to what was in the recipient ratios, and this actually translated into a similar amount of gender mismatch in both arms.

In terms of how the harvesting and transport and the transplantation occurred in the two arms, we've already heard that the out-of-body time or the cross-clamp time was substantially higher in the OCS lungs, of the OCS harvested lungs, not unexpected. It was about a 20 to 30% increase depending on if one is talking about the first lung or the second lung.

The average perfusion time, as you can see there, was a fairly long amount of time,

3 and 2/3 hours. And as was already mentioned, the cold ischemic time, and this is the second lung that I've highlighted there, was substantially longer, again, not surprisingly in the standard of care group.

One thing I will point out, though, is that the OCS arm had a higher surgical complication rate than did the standard of care. And an important thing to also consider is, as was alluded to by the Sponsor's presentation, is that the OCS lungs had an obligate two to three units of packed red blood cell exposures prior to arriving at the recipient hospital.

So this, then, is the Sponsor's primary effectiveness endpoint, again within 72 -- that is their preferred analysis -- and their inference is that it met non-inferiority. And this uses the per-protocol population, as they've explained why they feel that's appropriate, and you can see it meets the non-inferiority margin. As was mentioned by other speakers, superiority testing did not show superiority, however.

FDA's inference with this "within 72-hour endpoint" is different. We don't think there was a demonstration of statistical non-inferiority, and this is because we're using the modified intention-to-treat analysis, and we can see the treatment difference did not meet the performance goal success criterion of 4%.

Now, the difference between these two is related to protocol violations, and we'll get into those in just a little bit, but I want to step up again and just revisit the screen failures and discuss the implications of that in our opinion.

As already was mentioned, 14% of randomized subjects were screen failures, and most of them were in the one arm of the study, the OCS arm. We think that by virtue of this happening, that the randomization of the study was functionally lost, given the way the screen failures developed and their impact on the subsequent population, the modified intent-to-treat, the as-treated, and the per-protocol.

Perhaps more importantly is that 64% of these screen failures were still used, they

were still transplanted, those lungs and those patient combinations were still executed, and most of those screen failures with off-study use were OCS treatment arm to standard-of-care control arm crossovers. And these are patients, as was discussed somewhat before, for whom we have no real safety or effectiveness data to add to the totality of the data. So, almost by definition, we think that the screen failure rates have imparted a selection bias to this study.

So here, then, are those screen failures, and we were very concerned about this, and we looked at every single one of them and all the sources of documentation. And these are they, there. You can see what's the impact they had on the transplantation. The ones I've highlighted here in green, the ones on the outside, these are the ones that we expected would be screen failures. These were non-executed transplants, okay, and we agree that these did not add informative information to the assessment of the device.

But what about these? These are three OCS randomized patients who were transplanted using the OCS off study. We don't have data on these people. All of these patients, these were all patients transplanted off study with standard of care, and perhaps most illuminating is that 26 patients were transplanted off study, but they were crossovers. Again, we don't have these data, and this is frankly concerning to us.

So let's just take a look at a couple of these. I had mentioned the logistic screen failures is something that particularly caught our eye. And just to give a little flavor of -- you know, this isn't just theoretical in our opinion. We actually have some true concerns about what these screen failures might have done to the analysis population.

So this is a standard-of-care logistic screen failure. What it was, it was a patient who was fully consented. The harvesting team and the investigators were told that randomization was to the control arm. The preservation went ahead with the control arm, and the patient was followed off study for about 48 hours, as the protocol indicated.

However, it turned out that, in fact, through miscommunication, the envelope was never actually opened until 48 hours after transplantation, and that's when the envelope was opened, and it turns out the patient had been randomized to standard of care. But the investigator didn't know that; no one knew that this randomization did not actually occur per the envelope opening.

So the Sponsor heard about this at about 72 hours after the transplantation. Again, the investigators, the team harvesting had no idea that the patient was not randomized like this. But the company, if you can read there, determined again at 72 hours that because the envelope was opened late, that this patient was a screen failure. We were surprised by this determination, so we actually asked the Sponsor to clarify for us why this wasn't a protocol violation or a protocol deviation, and the Sponsor provided us with this distinction between the two, and we acknowledge that this is how they feel the difference was. But we believe that the distinction is problematic for the INSPIRE trial; it's almost a distinction without a difference because these are patients who were enrolled and treated identically, and yet, for the screen failures, we have no data on them, so the totality of the data is not total in our opinion.

Now, one can also debate whether the fact that the investigator didn't know about the randomization, whether *a priori* it fit that criterion of being a screen failure. But regardless, we felt, just on the merits, that this was a protocol deviation because it had minimal effect on trial outcome. And, in fact, there were multiple protocol -- minor protocol deviations during the trial involving randomization envelopes. And even that patient was characterized in the PMA submission by the Sponsor as a protocol deviation, and yet, it was also then determined to be a screen failure.

Let's look on the other side, a logistic screen failure on the OCS arm. This patient was excluded because the OCS device was not able to be powered up, and it was confirmed

that this was a device malfunction. We saw that in some of the interactions that the Sponsor had, that they felt it was important to note that this happened prior to the harvest because the timing of the device malfunction was key to the determination of it being a screen failure.

But in point of fact, we don't think that's correct because if you look at the carefully designed intent-to-treat definition, it says an intent-to-treat population is the lung has been harvested and it's eligible for preservation. Well, this lung was harvested, this lung was eligible for preservation, and it just so happens that it was a device failure. That does not, in our opinion, constitute a removal from the intent-to-treat population. It was a device failure. It can be taken care of in looking at the adjunctive populations, but it should've been, in our opinion, part of the intent-to-treat population.

So there are multiple donor screen failures, not surprisingly. Nearly two-thirds of them involved screen failures with off-study preservation, as I mentioned already. Here are a couple of them where we won't go into too much detail with them. One of them was -- actually had the determination of a screen failure made, it seems to us, by the Sponsor rather than the investigators prior to the final visualization of the lungs, and then the lungs were actually used for harvesting nonetheless.

One was a pediatric donor. We didn't see a lower margin for the donor age to be a reason for not including in the study, but it was applied.

There were some other issues. Donation after cardiac death, clearly a confounding aspect of the transplantation, but again not pre-specified in the trial, and that's a little problematic.

And then finally, I highlighted some of the donor criteria. One, I suppose, could debate whether the carnification pneumonia was active pneumonia because, again, the lungs were used; whether small infarcts in the lower lobes is active primary disease

because, again, these lungs were used.

So 40% of these donor screen failures followed by off-study preservation occurred at one site, and 9 of those 10 involved OCS to control arm crossover.

So I'll just go back. You know, with all of these screen failures, one might ask why is it that we think that there's any robustness in our inference of not showing non-inferiority? And so we did a tipping-point analysis of all those subjects who were transplanted off study, and there were 9 in the control arm and 28 in the treatment arm. And so down here is that none of them were actually successes. You can see that it's still not a demonstration of non-inferiority. And it would take 17 or 18 successes in the OCS arm and no successes in the control arm to change our inference of non-inferiority not being demonstrated.

So let's go back now, switch gears to the protocol violations, again going from the mITT population down to the per-protocol population. The populations differ, as you've heard, by 15 patients, 14 protocol violations, and 1 device failure that led to organ turn-down.

So here is that CONSORT diagram. You can see the seven instructions for use or user error protocol violations. Overall, we think that there was a low frequency of protocol violations for a study of this magnitude, and that's admirable. However, there was the imbalance, as was already discussed, and this imbalance occurred again despite 1:1 randomization. And a lot of what I'm mentioning is that this was -- we cannot forget that this was a 1:1 randomized study because a lot of the strength of the study was based on that 1:1 randomization, in our opinion.

When you look at the endpoint outcomes, among these 14 protocol violation patients, it's notable, in our opinion, that all of the OCS arm patients were endpoint failures while three-quarters of the standard of care protocol violations were actually endpoint successes.

And when you look at what constituted, in the protocol, a protocol violation, you can see the first three bullets there are very standard for a trial. The fourth one is a rather circular characterization of a major protocol violation, and it perhaps sets the stage, unfortunately, for this nebulous characterization of protocol violations, which we think might have had an impact on the per-protocol population.

So we did the same thing. We looked at every single one of these protocol violations and their source documentation. There was a device failure, which we discussed already. There were these instructions for use errors, again, not something I specifically identified in the protocol. I guess it falls under the other major protocol violations that these were considered to be protocol violations.

And so let's look then at a procedural protocol violation, which I'm calling an arterial blood gas time stamp protocol violation. So this is how the Sponsor characterized this protocol violation in 2015, after conclusion of the study, that there was no final P/F ratio blood gas to determine the eligibility of the donor lung. And we were a little surprised by this because, when we looked at the source data, we saw that there was a blood gas. It was at 8:30 in the morning and the transplant occurred several hours later. It actually occurred 4 hours and 25 minutes later.

We saw, though, that the Sponsor felt that since the blood gas was taken greater than 4 hours prior to cross-clamp, that this was equivalent basically to not being done and therefore the patient should not have been enrolled. We did not find this 4-hour time threshold in the protocol.

However, what we did find is that there were multiple other patients in the study for whom they had longer blood gas to cross-clamp times. Here's one that had 4 hours and 32 minutes, not a protocol violation. Here's one 8 hours and 50 minutes between the blood gas and the cross-clamp, not a protocol violation.

So let's do one other example, the active pneumonia. This was a patient who was transplanted in 2013. The patient unfortunately died roughly a month and a half later. The cause of death was congestive heart failure and was alluded to somewhat before. It wasn't just congestive heart failure; this was heart failure caused by injury to the left anterior descending artery that was necessitated for the evacuation of hematoma post-transplantation. So it was adjudicated as not being lung graft or device-related, but it's important to understand that this was a transplant-related death.

You can see here that the Sponsor, in 2015, wanted to clarify that there was an exclusion criterion of no active pulmonary disease and that it should've been -- no, that basically this subject was not appropriate for inclusion in the per-protocol population. And so we looked at the case report forms and we see that well, yes, there were mucoid secretions, which is what the Sponsor was invoking. There were no mucopurulent secretions, but again, the Sponsor felt that it was ineligible for the trial because of mucoid secretions. Again, we didn't see that degree of granularity in the protocol, that mucoid secretions would be an exclusion criterion.

So we actually looked at the source documentation for this patient. This is the donor run log for the harvest of these lungs, and as you can see, I've highlighted there the lungs appear to have been very appropriate for using. The bronch looked good, and the lungs looked good, and the bronchoscopy report from the harvest says that there was normal bronchi, mildly increased clear secretions.

Now, the rest of this harvesting was not quite so straightforward, unfortunately. There were the -- perhaps, unfortunately -- typical interactions between various harvest teams that can make a harvest somewhat challenging. There were logistical issues with the ground transportation, and perhaps most importantly, there were mechanical issues with the airplane to return to the transplant center, and this delayed return to transplant center

without death just delayed that. These are the type of things that do happen in a harvest. What you can see here from the donor run log, that the machine, the OCS machine was plugged in according to the harvest team and that the battery was reading 10 hours of life. And that should be fine because it was a 3-hour plane ride. Unfortunately, once they did get into the air, the battery life suddenly changed from 10 hours to 2 hours, and then en route, the device stopped working because of a battery failure. They arrived at the recipient hospital, plugged it in in the ambulance, and then immediately went up to do the harvest. In total, this lung was exposed to, it appears, roughly 15 minutes of warm ischemia time and had a stormy postoperative course.

This is the Sponsor's assessment -- I'll let you read that there -- that it was invoking the ineligibility of the lungs, user error for not plugging in the device, and the problems with the plane. What's missing from this, though, is a device failure. We spoke to the surgeon involved, and he did not think that there was any pneumonia present. FDA spoke to this individual.

What's perhaps striking though, to us, was that the very next patient at the same institution, when we looked at that case report form, actually had evidence, in our opinion, even though we're not appropriate to do the adjudication, of pneumonia. There's mucopurulent secretions. They did a bronchoalveolar lavage which showed evidence, it appears, of infection.

Now, this was a standard-of-care subject and was not considered a protocol violation during the data cleanup by the Sponsor, and this patient actually had a lung graft-related infection adjudicated against it. And this patient unfortunately also died peri-transplant.

So that patient was invoked using a procedural protocol violation, using donor eligibility protocol violations. We actually think that this wasn't a violation at all; this was fundamentally a device error and that that patient should be appropriately accounted for in

all the populations.

So I mentioned the two endpoints, the at 30 and within 72. As you've heard, the at 72 time point was the pre-specified endpoint based on PGD3 at Time 72. It was accepted, and I think still is accepted, to correlate with the clinical condition of recipient subsequently. The hypothesis was designed to account for only a single time point measurement, not the multiple time points. The analysis plan also had no interim analyses specified.

In December 2013, though, as you've heard several times now, after many of the patients had undergone transplantation, the Sponsor chose to change this endpoint in the protocol, and as was alluded to before, we strongly advised them not to do that because we were concerned about jeopardizing the integrity of the study given the amount of data that had been collected already. It's not that we disagreed with the value of Time 0, plus 24, plus 48, plus 72; we did not disagree that that has merit, and we still don't disagree with that. But in the context of the trial, we thought it was very problematic.

And so if we look at the pre-specified endpoint, what we can see is there's no demonstration of non-inferiority in either the per-protocol or the modified intent-to-treat analysis populations. And, again, it's with that 4% non-inferiority margin. You can see the actual upper bounds there, 8% and close to 12%.

So what constitutes the difference between at 72, within 72? Or are we just parsing numbers here? Well, when all is said and done, there are four endpoint population combinations. You can have the treatment effect in the per-protocol population based on within 72, based on the mITT population, and do the same with the as-treated. And as you can see, three of these four are not meeting the success criterion of 4%. Only the one PGD3 within 72 hours in the per-protocol population, the population most affected in our opinion by selection bias, shows non-inferiority.

When we break down the components of that death and PGD Grade 3, we see that clinically -- this has been mentioned already -- that the 30-day survival was better in standard of care patients. I say clinically because the p-value, this was actually the third pre-specified secondary effectiveness endpoint; it was not to be tested based on the hierarchical nature of it, but nonetheless, you can see the difference in survivals between the two. Then if you just show that on the Kaplan-Meier curve, it accentuates how the survival within 30 days appears to be better in the control arm.

In terms of the other component, the primary graft dysfunction graded at whatever time you choose to, you can see that primary graft dysfunction at T72, the original time point, was clinically pretty similar between the two arms in both the mITT and the per-protocol population.

However, when you look at within 72 hours, you can see that they're similar except for one notable difference -- is there any way to move it along? Oh, okay. Thank you. And that's the Time 0, and you can see a pretty striking difference, 21% versus 13%.

And so we think -- when you juxtapose the 30-day mortality with these data, we come to the conclusion that the Sponsor's inference of non-inferiority is driven almost exclusively by primary graft dysfunction at Time 0. And we think that's statistically less appropriate than looking just at Time 72, and that's because there's an unquantifiable alpha inflation due to the non pre-specified endpoint modifications based upon, or at least influenced by, unplanned interim analyses.

And when we say the unplanned interim analyses, we're not saying formal analyses by the Sponsor per se, but when you look in 2013, by the investigators -- this is from the ISHLT meeting -- you can see, up to 2013, they're talking about the study. And at T72 they're identifying no statistical difference in primary graft dysfunction Grade 3, but at T0 a substantial difference, and that's driving their T0 to T72 statistically significant difference.

Again, 1 year later, the INSPIRE investigators highlighting T72, not really a clinically significant difference, but at T0 a substantial clinical difference.

So that's the statistical argument, perhaps, for the T72 endpoint. What about just a clinical argument? Well, we can ask the Panel to discuss this, of whether the grade -- the primary graft dysfunction grade relationship to outcomes might be confounded in the early postoperative period by, for example, the use of cardiopulmonary bypass during the transplantation. There may be transient aspects at Time 0 that don't render it as sensitive or specific a marker as the later time points. And this isn't just our assessment; this is the 2016 updated ISHLT consensus statement, and you can see that for both they gave consideration to not using Time 0 because of confounding episode effects, and also, that the later time points are perhaps better in clinical trials.

Now, in terms of the primary graft dysfunction, this is a recapitulation of the 2005 consensus statement, and you can see these are the episodes that would result in a Grade 3 determination: P/F ratio less than 200 and the presence of an abnormal x-ray or any use of ECMO.

As you've heard already, the Sponsor, between 2013 and 2014, sought to streamline the PGD grading scale so that it would be perhaps more readily used throughout the trial. And in doing so, they added these caveats, in our opinion. The one, the extubation caveat, that if you're extubated, you cannot be PGD Grade 3, or 2 for that matter. And the second caveat was that if ECMO is pre-designated as prophylactic, then you're not automatically PGD Grade 3.

Now, we think that that application, with regard to INSPIRE, is not consistent with the ISHLT consensus statement, which was part of the protocol, and we think it's problematic for interpretability. And we don't think that adjudication by the medical monitor or DSMB member sufficiently removes that problematic problem for the

interpretability. And, in fact, if we thought that adjudication of PGD was going to be a contention, we would strongly recommend, as we do with many studies, to have a formal clinical events committee to talk about the adjudications and that they would look at the -- all of this was documentation, for example, the actual radiograph, to determine those endpoints.

This is not to say that we disagree with the notion that prophylactic ECMO is becoming more and more popular with transplantation and that it is in any way inappropriate to do that; we're not saying that at all. We recognize that. But we just think it's important to know that in the context of this trial, more OCS arm subjects were treated with the designation of prophylactic ECMO than in the control arm and that it's impossible for us to say, at this stage, that prophylactic ECMO doesn't actually prevent primary graft dysfunction greatly. It very well may, and that's what I would assume most people would want to have happen, but does that confound the interpretability of this endpoint? We think it does.

Similarly, this prophylactic caveat might lead to the censoring, if you will, of therapeutic ECMO, real primary graft dysfunction Grade 3 that everyone would agree upon, because there's no set way to define, in the Sponsor's implementation, what happens if prophylactic ECMO goes to therapeutic ECMO.

And then, finally, I'll just say that, regarding intubation status, we acknowledge that different clinicians, different investigators have varying opinions about what the extubation status should have with regard to the assessment of primary graft dysfunction. But the 2005 consensus statement does not include an extubation caveat; it is not in there. And perhaps more to the point is the revised 2016 update to those seems to agree with our interpretation. On the bottom it says that non-mechanical ventilation should not be considered differently.

Regarding ECMO, it states that non-primarily hypoxemic use of ECMO should be considered ungradable. And I'll just point out that they don't use the term "prophylactic"; they use the indication of ECMO primarily not for hypoxemia.

So, you know, we tried to assess what this change in the interpretation of the ISHLT 2005 grading scheme might mean to the trial. We did a very limited sensitivity analysis using the per-protocol population, and we went back and looked at all of the subjects who survived to Day 30, actually had a P/F ratio less than 200 within the 72 hours, so we're talking about within 72 hours, the Sponsor's preferred analysis, and yet were adjudicated as not being endpoint failures; they were not primary graft dysfunction Grade 3. And we reclassified them as primary graft dysfunction Grade 3, and what we saw is, if you can see it, that the Sponsor's endpoint up in the middle in the green seemed to move substantially, in our opinion, down towards that rejection zone of non-inferiority. So this made us think that the grading of primary graft dysfunction suggested that the robustness of the Sponsor's inference is not particularly high.

And to finish up, just more fundamental aspects: What about longer-term survival, 2-year survival? Not an endpoint, but we saw two things. First, an increased hazard of death, which we've already talked about, within 30 days, but we also saw no longer-term survival benefit out to 2 years with the device.

We even wanted to see if perhaps, if patients developed primary graft dysfunction, would use of the device have perhaps imparted a beneficial effect in terms of survival? And we didn't see that the device actually appeared to help with this. Now, this was a post hoc analysis, a very small sample size relative to the main population, but if anything, it would suggest that standard of care patients who actually developed primary graft dysfunction were faring better in the first year, year and a half.

So, in summary, the OCS lung is a first-of-a-kind preservation device. We fully

recognize its intuitive appeal to lung transplantation physicians because it's presumed to reduce ischemic reperfusion injury, and it clearly can help with the flexibility, if you will, of procurement during the harvest.

The trial had a complex but it was a reasonably constructed analysis plan from the outset. However, there were unplanned modifications to the primary effectiveness endpoint, in particular, that we think unfortunately have an impact on the trial's interpretability.

We do think that there was a selection bias present in the effectiveness results that have been reported.

Unquestionably, the device facilitated longer preservation times than cold static storage. But we don't believe that it demonstrated non-inferiority of effectiveness to that control arm in what we view as the key analysis population, the modified intent to treat.

Thirty-day mortality was higher in the treatment arm patients, and we didn't see any evidence of a longer-term survival benefit.

And then finally, and Dr. Bahadori is now going to discuss this, we did not see a particularly clear signal of decreased incidence of BOS out to longer term.

So thank you very much.

DR. SCHWAITZBERG: So, Dr. Bahadori, in the interest of time, if you could hit the high points and summarize in about 5 minutes.

DR. BAHADORI: Okay. I will probably end up skipping most of my slides. I am Lila Bahadori, and I am the pulmonologist with the Respiratory Branch in the Office for Device Evaluation, and I will present our review on the long-term data related to bronchiolitis obliterans syndrome and the safety data.

Now, bronchiolitis obliterans syndrome is the leading cause of morbidity and mortality in lung transplant recipients that survive beyond 1 year, and one of the interests

in this device was to see whether there would be any benefit to a freedom from BOS with this device. And TransMedics had also suggested that there was a higher probability of freedom from BOS in subjects that were treated with the OCS device versus controls at 24 months. So we asked them to actually capture the bronchiolitis obliterans syndrome data endpoints; however, this was actually not pre-specified as a safety endpoint.

And in the interest of time, I think we've already discussed the definition and the grading.

And so when we evaluated the Sponsor's data, and when we looked at both their BOS diagnosis and the Kaplan-Meier plots with the time to event of BOS at 5 years, we did not observe a difference between the two curves.

And in a post hoc composite that looked at both patients that are alive and patients that had a diagnosis of BOS, we found that there was an initial separation in the survival curve in the first 5 months, but then the curves were overlapping. And essentially, we did not find any data to support a benefit for freedom from BOS at 24 months.

Now I will discuss the safety endpoints for the INSPIRE study, and these were defined, the safety endpoint, as the average number of lung graft-related serious adverse events up to 30 days after transplantation. And the safety population was the primary analysis population; however, it did exclude the lung turn-down.

And in the interest of time, we've already heard the lung graft-related serious adverse events, and the definitions have been provided. Just to make a note, some of these definitions were actually updated in 2015 by both TransMedics and the medical monitor.

And I'm sorry, but I'm just going to skip over these. I just want to make a comment about the definition of respiratory failure that required re-intubation tracheostomy or the inability to be discontinued from invasive ventilation.

So when we looked at the table for the safety endpoint, this did make the

non-inferiority margin of 0.07; however, we should keep in mind that this did exclude the disproportionate number of screen failures.

Also, when we were looking at these lung graft-related serious adverse events, one of the things that was noted was that there was an increased incidence in the subjects of respiratory failure in the OCS arm versus the respiratory failure -- versus the controls. And the issue came up of whether this may also account for some of the early mortality that we had seen.

We also looked at the serious adverse events by organ system and found those to be comparable.

And so, in summary, we did not identify any data to support a true benefit for freedom from BOS.

The incidence of the adverse events by organ system was comparable between the two arms.

The pre-specified safety endpoint was met; however, those results should be interpreted with caution, secondary to the disproportionate rates of screen failure.

And then the incidence of the respiratory failure was observed to be higher in the safety population in the OCS arm, which raised the question regarding the early mortality.

Thank you.

DR. MIN: My name is Lauren Min, and I will be presenting the post-approval study considerations.

DR. SCHWAITZBERG: And your predecessors have left you 3 minutes to do so.

(Laughter.)

DR. MIN: Okay, let's try this. Based on review of the premarket data, the FDA review team identified these postmarket issues.

And to address these issues, the Sponsor has proposed two post-approval studies

listed here.

The extended follow-up PAS seeks to evaluate patient survival, cause of death, and BOS up to 5 years, and no other information was provided for this proposal.

We agree that leveraging the INSPIRE cohort to get 5-year data on the proposed endpoint is the most efficient way to obtain long-term data. However, INSPIRE subjects were consented for 2 years, and so there are some limitations with obtaining re-consent on the patients for additional follow-up; namely, long-term results may be confounded by under-representation of sicker patients and missing data and the time gap between the INSPIRE trial and the post-approval study.

The Sponsor is also proposing a new enrollment study of a single-arm study of data collected in the OCS thoracic organ perfusion registry. This study seeks to evaluate short- and long-term safety and effectiveness of the device in U.S. patients.

This is another overview of the study design.

FDA believes that a new enrollment PAS is needed to overcome key issues in the design conduct and analyses of the pivotal study and to provide a clear picture of device performance in the U.S. population. However, we recommend that TransMedics leverage the existing UNOS registry as UNOS already captures high-quality data on the outcomes of interest. And given that the INSPIRE data from U.S. participants were collected through UNOS, TransMedics is already familiar with this registry.

The Sponsor proposes to test the hypothesis that 5-year survival is greater than 38.4% based on a point estimate of 50.4% with a 12% margin. The 50.4% survival was based on OPTN data of double-lung transplants performed between '97 and 2004. We believe that this point estimate is too low based on improved survival in more recent years. A 2015 annual report from OPTN reported a 5-year survival of approximately 60%, and we believe that this is a more appropriate point estimate.

In addition, the additional proposed outcomes are listed here. While FDA supports collection of PGD data at all key time points, we recommend evaluation of PGD Grade 3 at 72 hours for outcome assessment.

The Panel will be asked to discuss the appropriateness of the proposed outcomes and follow-up assessment in order to evaluate the short- and long-term safety and effectiveness of the device.

Lastly, the Sponsor did not specify a primary safety outcome. FDA recommends this be the incidence of lung graft-related adverse events up to 90 days post-transplant, including acute rejection, respiratory failure, pulmonary-related infection, and bronchial anastomotic complications. It is unclear whether lung graft-related events should also be evaluated beyond 90 days.

The Panel will be asked to discuss an appropriate primary safety outcome including the time period and an acceptable margin.

This concludes FDA's presentation.

DR. SCHWAITZBERG: You just squeaked in there. Thank you.

In the interest of time, I would ask the panelists to confine their questions to the presentation for clarification. We will get into the philosophic debate of the groups and the appropriateness in the deliberations. So questions about the actual presentation, and we'll start on this side of the table with Dr. Afifi. Just clarifying questions only, please.

DR. AFIFI: No questions.

DR. SCHWAITZBERG: Thank you.

DR. YUH: David Yuh.

How was the inferiority margin of 4% arrived at? The Sponsor made an issue about that, and I just wanted to get your rationale for arriving at that number.

DR. SAPIRSTEIN: So I'll just give you a quick overview of how FDA works with a

non-inferiority margin.

DR. SCHWAITZBERG: Can you bring the microphone closer? We can't hear you.

DR. SAPIRSTEIN: Yeah, sorry. I'll just give you a quick overview of how FDA deals with a non-inferiority margin, and then I'll let some other folks who were involved with the actual negotiations go into it.

Every non-inferiority margin is different for every device and every study. There is no standard that 15% or 10% or 5% is appropriate for any given cardiovascular device or thoracic device. In this particular case, there were negotiations between what would constitute an appropriate endpoint in terms of mortality and graft dysfunction. And then when those specific components were decided upon, there was a consideration given to what would be both a doable statistical study as well as something that could provide clinical support for, in this case, non-inferiority.

DR. GONZALEZ: Yes. Hi, I'm Gema Gonzalez. I am a reviewer with the Renal Devices Branch. And so when we were designing the clinical study or reviewing the clinical study for the IDE, we were considering the fact that these were standard criteria lungs in terms of being eligible for transplantation, and the success rate that was proposed for the control group, based on the endpoint that was being discussed at the time, was 94%. And we felt that with a high margin of comparison between the two groups, that would bring the success rate for the OCS arm to be unacceptably low, clinically speaking. And so that's where we were considering the patient population and the type of organs that were being used in the study and what would be clinically significant as success for the OCS arm.

DR. FISHER: Non-inferiority versus superiority?

DR. GONZALEZ: Yes, thank you. And, of course, we were also considering the fact that it was a non-inferiority study design as opposed to superiority, so that was another factor, the consideration.

DR. SCHWAITZBERG: Clarifying questions, Mr. Riley?

MR. RILEY: No questions.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: Roger Yusen. No questions.

DR. NATHAN: Steve Nathan.

I do have a question. When the Sponsor or whoever it was that made a decision with regards to a screen failure or a protocol violation, they obviously, at least in most cases, knew which assignment the patients had received. Were they blinded to how the patients did, to the outcomes? And at what point did they make a decision to call it a screen failure versus a protocol violation?

DR. SAPIRSTEIN: Yes. As I had suggested, we were confused ourselves when we were viewing the data of when this threshold for designation of screen failure or protocol violation actually occurred. It appears that, from our understanding from the Sponsor's clarifications, that a screen failure occurred at the time of the harvesting, whereas a protocol violation appeared to have been designated, from our review, upwards of 2 or 3 years after conclusion of the transplant.

DR. SCHWAITZBERG: Thank you.

Dr. Meyer.

DR. MEYER: I have one quick question. Dan Meyer.

The screening failures and the conversion of those to crossovers, what would the FDA feel would be the -- how would that affect the integrity of the study, if indeed those screening failures were converted to crossovers and an analysis re-performed?

DR. FISHER: This is Ben Fisher with FDA.

I think that actually we're going to ask you guys this afternoon how you feel about that.

DR. SCHWAITZBERG: All right, let's move on.

DR. MOON: Are the slide numbers the same as we got in the pamphlets? Because I'd like to see Dr. Sapirstein's Slide 70, I think, because I don't think the numbers match.

DR. SCHWAITZBERG: While he's putting that up, Ms. Barnes, do you have any clarifying questions?

MS. BARNES: I don't.

MR. FRANKEL: Z. Frankel.

Just a couple of clarification questions from FDA regarding their position, one being that the Sponsor had asserted, based on studies, that PGD at T0 correlates with long-term BOS risk; I wanted to know whether the FDA agreed with that position.

Also, the FDA noted that there was no long-term survival benefit, on one of the last slides, when comparing the two arms. Was there any other clinical benefits noted amongst that patient population? Was that looked at in terms of those that survived?

And, finally, the Sponsor noted difference of opinion with the FDA regarding PGD grading criteria. I wanted to know, regarding the FDA's position, why they differed from the Sponsor, just a little bit of elaboration on that point.

DR. SCHWAITZBERG: So we'll get into the philosophic differences after lunch, but did you have a question about what he actually presented? But I promise you, we'll get to the philosophy after lunch.

DR. SAPIRSTEIN: So if you're asking about the -- did we see any other clinical benefit --

MR. FRANKEL: Yes.

DR. SAPIRSTEIN: -- of the device? We actually requested post hoc analyses of many different approaches to assessing the clinical benefit based on whether you saw one from the Sponsor on the duration of ischemic time, whether there was a clinical benefit for

longer ischemic times, whether there was a clinical benefit among patients with longer ischemic times who went on to develop primary graft dysfunctions. We looked at multiple different post hoc analyses. They were obviously hampered by the post hoc nature and the smaller sample size, but to answer your question briefly, we didn't see a resounding clinical benefit in any of those.

MR. FRANKEL: So it's roughly the same as no difference in terms of survival benefit?

DR. SAPIRSTEIN: Correct.

MR. FRANKEL: Okay, great.

DR. SCHWAITZBERG: We can go back now to Slide 70. You had a question concerning Slide 70, or is that the wrong slide?

DR. MOON: That's the right slide, but these are not numbered correctly on our sheet, so it's hard for me to go back and evaluate this. So next time, let's get the numbers right.

DR. SCHWAITZBERG: All right, we'll keep moving.

Mr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla.

One clarifying question: So on the post-approval study that was just presented, FDA recommends evaluation of PGD3 at 72. Would it be better to have it as T48 and/or T72 to be consistent with the 2016 consensus statement? Thank you.

DR. SAPIRSTEIN: Well, again, I'll reflect, I think this is part of the reason we're here today, is to decide -- get input from the Panel about how exactly, knowing what we know now, how should we --

DR. SCHWAITZBERG: You've got to speak into the microphone.

DR. SAPIRSTEIN: This is exactly what we're asking the Panel to provide us guidance with, about knowing what we know now, what should we be looking at for primary graft

dysfunction?

MR. THURAMALLA: Okay, one other minor point: So can you cite any other comparable device trials which also had a non-inferiority criteria of 4%?

DR. SAPIRSTEIN: Well, again, I can go and look, if you would like. There are device trials that -- for example, the ENDURANCE trial was mentioned by the Sponsor and discussed it being 15%. I have a lot of interactions with the ventricular assist device studies, and in point of fact, we don't just arbitrarily say 15% and that's the way it was done. We often have sliding non-inferiority margins that are substantially smaller based upon what the actual point estimates for the two arms are.

Now, this wasn't done in this trial, but as you just heard Dr. Gonzalez talk about, we were concerned about ascribing a large non-inferiority margin that, at the end of the day, was going to be clinically not embraced by physicians. So I can look if you would like, but it's almost not germane to what we're discussing here because this was an agreed-upon non-inferiority margin.

DR. FISHER: This is Ben Fisher, FDA. I just want to follow up on that.

The Sponsor presented a composite of different margins and different studies. So I'd just like to point out that there was only one study that was on that composite that was actually a lung study. So Dr. Sapirstein had said, you know, we base our judgment on the devices and their indications, right? And kind of mixing apples and oranges there, the other lung that was on there was an HDE, and you only have to show probable benefit. It's not the same as a PMA. Okay, so there's a lot of variation.

DR. SCHWAITZBERG: I'm sure we'll get back to that.

Clarifying questions, Dr. Connor?

DR. CONNOR: None.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: No questions.

DR. SCHWAITZBERG: Mr. Stammers.

MR. STAMMERS: Al Stammers. Thank you very much.

Just a quick question: When the primary endpoint was modified, which clearly has brought up a lot of discussion in this session, and the FDA raised their considerable objections, did you have the ability to reject vehemently and actually say we're halting the study until we could decide conceptually what we should do?

DR. SAPIRSTEIN: No.

MR. STAMMERS: Thank you.

DR. SCHWAITZBERG: Sasha.

DR. KRUPNICK: A quick question regarding the Time 0 PGD. Do you have any data on unplanned use of cardiopulmonary bypass on what should have been a sequential single-lung transplant for the second lung between the two groups?

DR. SAPIRSTEIN: No, we don't have those data. And the Sponsor can discuss that certain sites used cardiopulmonary bypass routinely. There's debate obviously within the transplant community about whether that's appropriate or necessary. But certainly it was left to the individual sites to decide about the use of cardiopulmonary bypass. In terms of emergent cardiopulmonary bypass, no, I don't have those data. Perhaps the Sponsor does.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: Victor van Berkel from Louisville.

And this is perhaps going to fall into the homework category for maybe both groups, but looking at the two presentations, on Slide 133 from the FDA, which is on page 67 of our handout -- speaking to Dr. Moon's problem -- on Slide 133 of the FDA and Slide CO-64 from the Sponsor, they're looking at essentially the same data and coming up with very different numbers, and I don't quite understand why those two things are so different from one

another. My interpretation of looking at them is that they're looking both at the same set of data but coming up with very different percentages. And so I would just like some clarification on that.

DR. SCHWAITZBERG: So we can address that after the break so you have time to review it.

Dr. Hammon.

DR. HAMMON: No questions.

DR. SCHWAITZBERG: I just have one question. Is that -- well, I'll pass. We'll move on to lunch.

It is now 12:24 instead of 12:00, and we'll break for lunch. Panel members, please do not discuss the meeting topic amongst yourselves or members of the audience. We'll reconvene in this room at 1:05 sharp, so we got to eat quickly. And please take your personal belongings. The room will be secured, and we will start immediately with the open hearing.

(Whereupon, at 12:24 p.m., a lunch recess was taken.)

A F T E R N O O N  S E S S I O N

(1:05 p.m.)

DR. SCHWAITZBERG: It is now 1:05, and I would like to resume this Panel meeting. We will proceed to the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data and information or views relevant to the meeting.

Ms. Aden Asefa will now read the Open Public Hearing disclosure process statement.

MS. ASEFA: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with a company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

FDA has received 15 requests to speak prior to the final date published in the *Federal Register*. Each speaker will be given 3 minutes to speak.

DR. SCHWAITZBERG: Terrific. Before we get started, I'm going to name three speakers at a time so that you can be ready to go from the moment that we finish with our last speaker. I'm going to start the clock shortly thereafter, so please be up and be ready to

speak, and please do not be offended if at the end of the 3 minutes your time is truncated because we have a lot of material to get through.

There is one speaker on the *Federal Register* list that is not present: Dr. Albert Faro will not be speaking. The first speaker will be Dr. Matthew Hartwig, the second speaker is going to be Ms. Susan Gunderson, and the third speaker will be Dr. Marshall Hertz. So speakers 2 and 15 have been flipped.

So, Dr. Hartwig, Ms. Madsen [sic], and Dr. Hertz, if you can please get yourselves ready, and Dr. Hartwig, your time starts.

DR. HARTWIG: Okay, thank you. Good afternoon. Thank you to the Panel for providing me the time to speak today. My name is Matthew Hartwig. The perspective I will be giving is that of a lung transplant surgeon, which in some way is one of the end users of these types of devices.

My disclosure: My travel was paid for by TransMedics today. I think they provided about $250 in salary support because we participated in one of their trials. I also have some salary support from the XPS XVIVO trial.

I'm the Director of Lung Transplantation at Duke. Our transplant program is considered to be a heavy utilizer of donated lungs. Over the last 5 years, our program has done more transplants than any other lung center in the country. I think more important for this discussion is that our center is experienced with the clinical use of EVLP, and we participated in the NOVEL trial, or NOVEL trial, evaluating the use of the XPS acellular normothermic preservation system and participated in the extension trial of that device. We did not participate in INSPIRE, and I have no inside knowledge of that trial, but we did have the opportunity to use the OCS firsthand clinically in the tail end of the EXPAND trial.

So, firstly, I'd like to emphasize that early pulmonary allograft dysfunction, or PGD, does remain a very significant problem for our patients and an expensive problem for our

healthcare system. We know that modern ICU and mechanical support devices such as ECMO can keep very sick patients alive, even those with severe PGD, for an extended period of time and that 30-day survival is really not the best measure of perioperative outcomes anymore because of that.

But we also know that even if patients survive the period of early graft dysfunction, that it can be associated with severe financial, emotional, and physiologic costs long-term on the patients and their families and the healthcare providers and the healthcare system.

And so I firmly believe that a significant portion of the disappointing 1-year survival that we see in lung transplantation is, in reality, simply an extension of some of these peri-transplant issues that are no longer detected in the 30-day risk.

So having had the opportunity to use the different devices clinically, I'd just like to comment on a few first impressions of the OCS system. Importantly, you know, this is not meant to be a comparison at all between devices or to suggest that one technique is superior to another. One of the first things that we noticed was an apparent ease of use of the OCS, and it seems to be designed in a way to minimize opportunity for human error to be introduced into the system. And it appears to be a device, much like the newer ECMO machines we use, that different members of the healthcare team can be trained to monitor and maintain with minimal effort. I don't know if subtle changes have occurred in the device between INSPIRE and EXPAND, when we were using it, but our team's impression was that lung transplant personnel of various levels could be taught in a very short period of time how to use the OCS system and that it could be set up and maintained with the same type of procurement teams that we currently use.

I think the ease-of-use feature lends some credence to a second observation, which is that the OCS system appears to be a very stable platform. In my mind, that's the critical feature if we were discussing the possibility of ubiquitous use of any device that's going to

be used to maintain organs, organs that we consider to be acceptable for transplant. If we put a usable organ on the machine at the prescribed time, in the immediate future when that recipient is ready, that organ still needs to be usable. And I hope that the Panel spends a lot of time on this question and ascertaining from the data available whether an appropriate lung is placed on any device, that that device can maintain it regularly and reproducibly for transplant.

I don't know what's required for approval, but being able to show that the ex vivo maintenance of acceptable lung allografts may be superior to standard cold storage --

DR. SCHWAITZBERG: Please conclude.

DR. HARTWIG: Okay. I think that if the data do show that the PGD rate is, in fact, decreased by this device, that that would be critically important and, in fact, the first time that that's ever been shown in a randomized controlled trial. And so I'll be very curious to see how the Panel reviews the final data.

DR. SCHWAITZBERG: Thank you.

DR. HARTWIG: Thanks.

DR. SCHWAITZBERG: Ms. Gunderson.

MS. GUNDERSON: Thank you, Mr. Chair and Committee members. My name is Susan Gunderson. And for the last 28 years, I have served as founder and CEO of LifeSource. We're the organ procurement organization serving Minnesota, North and South Dakota. Just in terms of professional experience, I'm also a past president of the Association of Organ Procurement Organizations, president-elect of the International Society for Organ Donation and Procurement, and with UNOS have served on the board of UNOS and as an officer of UNOS.

Being in Minnesota, we also have had an opportunity to work with the OCS system in collaboration with the University of Minnesota, a lung transplant program, so our organ

recovery team has worked in partnership.

And just a couple of key points: In our experience, it has been relatively easy to learn the skills to use this device from our perspective, and most importantly, it is not disruptive to the standard organ donation process. So that's an important point, I think, the Committee might want to consider.

I don't think I need to remind this group of the ongoing and growing gap between the availability of organs for transplantation and the number of people who need them. That gap continues to grow each year, and while there are many individuals and organizations working through multiple strategies to try and close that gap, to me, one of the greatest opportunities to increase the number of transplants is to increase utilization of the organs that we already have. Right now, only 20% of deceased organ donors are able to successfully donate lungs for transplantation, 20%. We can do better than that. And this kind of a technology, to me, provides the greatest opportunity for those increases.

The innovative process of ex vivo organ preservation is one of the most promising developments that holds great hope to really change the paradigm of organ recovery. And from the organ donation process and bigger perspective, I want to just make a couple of key points.

First, nearly all donation recoveries involve multiple recovery teams: a heart team, a lung team, a liver team, maybe a kidney and pancreas team. So there's lots of moving parts and a lot of coordination.

So any time and any flexibility in the OR timing that we can gain based on increased tolerance for preservation time will improve overall case effectiveness, not just for the lung system but for all of the other organs that are being donated at the same time.

This type of technology will also allow us to make offers for organ transplants to patients in broader geographic areas than we've had in the past. Distance will not be as

critical as it has been in the past.

And, thirdly, we make organ offers based on the best available donor information that we have, but having technology that not only provides additional evaluation information but also the potential to actually improve function will be really important to help us utilize the organs we already have. As the donor pool gets older, we use donors with more comorbidities.

DR. SCHWAITZBERG: Ms. Gunderson, please conclude.

MS. GUNDERSON: Thank you, I will. And we use DCD donors as well. So on the face of the growing organ shortage, the ability to increase organ utilization through more efficient recovery and improved organ function will lead to more lives saved.

And I should also say that I do not have any financial relationship with TransMedics. They did provide for my cost to travel to this meeting.

Thank you for the opportunity to present.

DR. SCHWAITZBERG: After Dr. Hertz, it will be Ms. Krushelniski, Dr. Johnson, and Dr. Fox-Rawlings. Please confine your comments to 3 minutes because I will cut people off so that everybody has the same fair chance. Thank you.

DR. HERTZ: Thank you very much. Good afternoon, ladies and gentlemen. I'm Marshall Hertz, and I am the Medical Director of the Lung Transplant Program at the University of Minnesota. I have been a co-PI, a co-investigator in the INSPIRE trial and the ongoing or the second EXPAND trial of the OCS system.

I have no financial or equity interest in TransMedics. They did provide travel support for this meeting.

By way of background, I've been the Medical Director of the U of M Lung Transplant Program since we started the program in 1986, and fortunately, I've gotten to the age where I can offer historical perspective.

During the early years, we almost immediately became aware of many donor-related challenges, including: number one, limited supply related to demand; number two, inability to provide truly national sharing of organs, which has been a high priority of the Department of HHS and other federal agencies. And also we haven't, of course, been able to physiologically support and treat lungs so that they can be rehabilitated and optimized before transplantation. And as you've heard, the TransMedics system addresses these longstanding shortcomings and has been shown to be user friendly, safe, and very reliable.

Although the EXPAND trial is not specifically being examined today, I will offer that our own center-specific experience in that trial showed a number of clear instances where lungs that were marginal or at the boundary of acceptability have shown improved function while on the OCS device and have been able to be successfully transplanted after transport on the device.

And, finally, I'd be remiss if I didn't applaud TransMedics and their outstanding team, which has worked with us and all of its investigators very closely. I've been very effectively -- rather, I've been a participant in planning, execution, and analysis of many clinical trials sponsored by many companies, and I can say definitely that from protocol development to center selection and contracting, to training, real-time support of our people, the TransMedics team has been first rate.

DR. SCHWAITZBERG: Thank you.

DR. HERTZ: Thank you very much.

DR. SCHWAITZBERG: Thank you for being on time.

Our next speaker is Ms. Brandi Krushelniski. And I'm sorry if I didn't get your name right.

MS. KRUSHELNISKI: You did perfect, thank you. I'd like to thank the FDA panelists for allowing me to speak to you today. I do not have any financial obligations or relations

with TransMedics. They did support my travel for today.

I'm Brandi Krushelniski. I am the Vice President of Transplant Services for St. Joseph's Hospital and Medical Center in Phoenix, Arizona. I've overseen the lung transplant program for 11 years, and we recently celebrated our 10-year anniversary coupled with the largest volume center in the United States performing 114 lung transplants in 2016. In addition, we've also received the highest quality rating of 5 out of 5 from the Scientific Registry for Transplant Recipients.

Using the Organ Care System for a lung in INSPIRE for standard organs and the EXPAND trial for marginal organs has allowed us to transplant 19 patients that might otherwise have died awaiting transplant if it were not for the use of the Organ Care System.

The wait time at our center is less than 2 weeks, and for patients that are on lifesaving machines in the intensive care unit or within hours of death, the Organ Care System has allowed us to accept organs that otherwise would not be salvageable. Our average length of stay between the two trials showed a reduction of 6 days for patients transplanted on the Organ Care System device versus those on the traditional standard of care. In addition, these patients use less ECMO and less intensive care unit days.

As a result, we realize significant savings within our global rates from commercial payers compared to the standard of care. Patients using the Organ Care System device netted 65,000 more per case than the standard of care organs, which is a direct revenue to the hospital that more than covers the Organ Care System device cost. In addition, our supply costs such as pharmacy, blood products, lab, radiology, and other ancillary services were also significantly reduced.

In summary, the Organ Care System benefited our patients with improved outcomes, shorter wait time list, reduced length of stay, and most importantly for the patient, the ability to return home sooner and accelerate back into their work, family, and community

endeavors. Our hospital benefited from the Organ Care System with an improvement in the financial performance in a very complex labor-intensive population.

For these reasons and more, I believe that a denial of the Organ Care System use from the FDA would be detrimental to lung transplant patients and the transplant centers. I respectfully request to please approve the Organ Care System Lung device.

Thank you.

DR. SCHWAITZBERG: Thank you.

Dr. Johnson.

DR. JOHNSON: Thank you. And my only financial disclosure is that TransMedics did support my travel.

I'm actually a heart failure transplant cardiologist, and you might wonder what I'm doing up here standing, but my career has really included things beyond my own professional involvement. I was a faculty member for the Organ Donation and Transplant Alliance. I was past president of the American Society of Transplantation. I've been secretary of the UNOS OPTN board and, most recently, president of the International Society for Heart and Lung Transplantation. However, I come today presenting my own opinions, not any of those organizations.

As of Monday of this week, 1,416 people are on the OPTN lung transplant waiting list. Indeed, in 2016, 335 candidates, nearly one-quarter of the current list, died or were removed from the waiting list because they got too ill prior to receiving a donor organ. As Susan said, in 2016 less than 20% of organ donors were lung donors, and if there were more donors available, particularly if we could extend ischemic time and test lung viability such as occurs with the Organ Care System, we should do this. Indeed, shouldn't we do everything possible we can to provide donor lungs for as many people as possible?

And now look at the things from the perspective of an organ donor family. After

losing your loved one and the decision has been made to donate their organs, wouldn't you want to optimize their use and the outcomes in the recipients? And if you're the recipient or the recipient's family, wouldn't you want everything possible done to improve the chances of a long and meaningful life?

Early outcomes following lung transplantation have improved with 80 to 85% of patients surviving 1 year. However, at 5 years it's down to around 55%, and only 20 to 30% will survive 10 years. Long-term outcomes after lung transplant still sorely lag behind those of other organs. And, indeed, the most common cause of death greater than 1 year after transplant, the cause of 20 to 30% of those deaths is bronchiolitis obliterans syndrome.

In all medical fields, but especially transplantation, doing well is not enough. We always have to strive to do better. We need to take every opportunity to honor the gift of the organ donor by transplanting the donated organs and optimizing recipient outcomes. The field and our larger community deserves no less and should accept no less.

The TransMedics lung OCS system decreases ischemic time, slightly improves the condition and oxygenation capacity of the lung, and decreases primary graft dysfunction at 72 hours, all significant achievements. It also showed a trend towards decrease in 2 years of bronchiolitis obliterans syndrome, as I've mentioned, the primary cause of death.

With these benefits, the field of lung transplantation deserves the opportunity to continue to use this system to further improve lung utilization and post-transplant outcomes.

Thank you.

DR. SCHWAITZBERG: Thank you.

After Dr. Fox-Rawlings, it will be Ms. Pusateri, Dr. Villavicencio -- and again, my apologies if I didn't get that right -- and Mr. Stoker.

Dr. Fox-Rawlings.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today. My name is Dr. Stephanie Fox-Rawlings. I am a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data to provide objective health information to patients, providers, and policymakers. We do not accept funding from drug or device companies, so I do not have any conflicts of interest.

There is a need for better outcomes for patients undergoing lung transplants. New devices and/or methods should be tested. It is difficult to design clinical trials to test ex vivo pumps; however, it is necessary to demonstrate effectiveness and safety for intended use of these pumps before approval.

The INSPIRE trial was intended to demonstrate the equivalence of TransMedics' Organ Care System to the current standard of cold storage; however, the trial had significant design and implementation problems. As a result of these flaws, it could not show that OCS was as effective as the current standard of care.

The INSPIRE trial had numerous opportunities for unintended bias to be introduced to make the OCS appear more comparable to control: (1) Some studies' sites disproportionately conducted surgeries for one arm, so differences in site conditions that were unrelated to OCS versus cold storage could alter outcomes; (2) The high number of off-study transplantations in the OCS arm is concerning. Since this study couldn't be double blind, the difference in off-study transplantations could be caused by doctors moving lower-quality lungs off study instead; and (3) the criteria used to define screening failures and other protocol violations were not consistent between arms or sites. For example, FDA scientists identified examples of OCS lungs that could be not used for study due to active donor lung disease, but similar cases were allowed for the control arm. Seventy-four percent of screening failures occurred in the OCS arm, which often led to off-study transplants. This could obviously bias the results. It would not have to be intentional.

Doctors in the OCS arm could unconsciously tend to avoid situations that would result in poorer outcomes.

Most important, the OCS did not meet the non-inferiority effectiveness endpoints designated before the trial started. To meet the primary effectiveness endpoints, both the analyzed population and one of the co-primary endpoints had to be modified. This occurred after unplanned analysis that the FDA advised against. This type of post hoc manipulation of data does not meet acceptable scientific standards needed for clinical trials. It would not be ethical to rely on post-approval studies to demonstrate efficacy and safety. Post-approval studies --

DR. SCHWAITZBERG: Please conclude.

DR. FOX-RAWLINGS: -- for devices tend to be small and delayed, and the proposed new enrollment study is based on a registry, so it's difficult to compare.

Thank you for your time.

DR. SCHWAITZBERG: Thank you.

Our next speaker is Ms. Lee Ann Pusateri.

MS. PUSATERI: Yeah, you got it. Hi, I am Subject 64, also known as Lee Ann Pusateri. I have no financial relationship with TransMedics, other than they paid for my travel.

In 2009, at the age of 43, I was diagnosed with pulmonary fibrosis, and I was given 3 to 5 years to live. I had a 3-year-old daughter and a 6-year-old son. For the next 5 years I watched my lung function slowly decline from an initially diagnosed 70% down to 25%, and by 2014 I was on oxygen full time. I had no choice left but to get a lung transplant.

When I was asked if I wanted to participate in the OCS trial, INSPIRE trial, I didn't hesitate. Actually, my husband didn't hesitate. He said, yes, we'll participate, and I looked at him, like, who's we, right?

(Laughter.)

MS. PUSATERI: I had a long time of evaluating -- experience evaluating other medical technologies, and I didn't see any downside to using the system.

In October 2014 I was on oxygen full time, and I had several months to live, and I couldn't walk from me to you without almost passing out. My little girl said to me one day, "Mommy, can Daddy not pick me up from school anymore?" And I asked her why, and she said, "I'm afraid when I get in the car he's going to tell me you died." She was 8 years old, and every day she went to school and worried Mommy would die.

Fortunately for me, on October 19th, 2014, I was randomized to the OCS arm, and I got my lungs 2½ years later, and I'm here speaking without taking another breath. You guys can see how long I can hold my breath now. My grafts are all widely open; they were open at -- I don't know -- I'm going to say T0, 24, 48, and 72. I can exercise every day. I skied at 4 months post-transplant at 11,000 feet and continue to do so every single winter.

But I'm going to tell you here, look, on October 19th I left my driveway, and my 8-year-old and 11-year-old were waving while I drove away, with tears in their face but totally excited that Mommy was getting lungs. And several hours later when I was on the table, my disease was so advanced that the surgeon told me later it was very difficult to get out the lungs. They were sticky, they fell apart, they couldn't come out, they couldn't -- he couldn't get them out very quickly. I am so grateful that he had the comfort and safety of knowing that he didn't have a clock of 4 hours to get in the lungs under the current standard of care. And I want every single patient's family to have that comfort, knowing if something goes wrong in the procedure, we're not talking about 80% of the time, if something goes wrong in the procedure, that surgeon can take a breath and relax and do it the right way for everybody's family and kids.

Lung transplant patients often trade one set of problems for another. But rarely is there a technology available that does not come along with the myriad of adverse side

effects that we have every day from the medications that we take to prevent rejection. I firmly believe that OCS is one of those advancements, and I urge you to please approve these.

Thank you very much.

DR. SCHWAITZBERG: Thank you very much.

Our next speaker is Dr. Mauricio Villavicencio.

DR. VILLAVICENCIO: Good afternoon. I'm the Surgical Director of Lung Transplantation from the Mass General Hospital. I was formerly founder and Chief of the National Cardiopulmonary Transplant Service in Chile, and I'm South American, and I'm still learning how to, you know, talk English.

And I just wanted to tell you that I look quite awful today. I look quite awful because I was up all night doing a transplant, and that's the truth, that we with the standard of care with cold preservation, we do the transplants in a hurry. We have 6 hours to implant the lung, and that's something that, you know, for a surgeon, it's usually a big problem. Probably after you get more experience, it's a little bit easier to get through. But having the lungs on the device is something that is really important.

I have seen some patients that have died, you know, in my hands or the other surgeons that, you know, they have been stuck, you can't get the lance out, but you wait hours and hours and hours to try to take them out or you try to take them out quickly, and then, you know, it just bleeds or gets massive transfusion and primary graft dysfunction. So having TransMedics with the lance, you know, perfused during that time, it is something that is really important. I have to tell you that since I came to the Mass General, we have increased the number of lung transplants more than 200%, and part of that is just the use of the TransMedics device. We have used it, in the last year, for example, in 25% of our cases. We did 40 lung transplants last year, and 25% of them was the TransMedics device. I would

say that it's very easy to use. I mean, many of us, you know, went over there and got trained, and it's very quick, and it's very easy. And, of course, we got a lot of support when we have questions, what we are -- you know, we have something new that we don't know how to use it properly.

So I think, you know, that increasing this amount of lung transplants 200% and have been able to doing that with 0% mortality has been, you know, really great success for us and, I think, for the New England region.

I have to say that I really believe that it produces less primary graft dysfunction. I think it's really important that primary graft dysfunction T0 to T24 or T48, because it relies on, you know, the long-term prognosis, I think when you just measure T72, you have --

DR. SCHWAITZBERG: Please conclude.

DR. VILLAVICENCIO: -- a lot and then, you know, it's not as good of a measurement as we have all of the timeline. So I will highly recommend to use TransMedics device.

Thank you.

DR. SCHWAITZBERG: Thank you so much.

After Mr. Stoker, we'll have Charles Alexander, Dr. Gregory Cosgrove, and Dr. Michael Smith.

MR. STOKER: Hi, my name is Robert Stoker. To disclose, I have no financials with TransMedics, but they did pay for my travel down from New Hampshire.

Just, you know, as to who I am, I am, number one, a lung transplant patient; number two, a father of one, and I was told I'd never see my daughter get married, and we're still waiting for that but --

(Laughter.)

MR. STOKER: After my diagnosis with alpha-1 antitrypsin deficiency, basically told that's it -- don't -- you know, whatever. Nothing's going to happen here. Luckily, I found a

really good transplant program out in Cleveland that said, hey, we'll take you on. You know, you're big and robust and you're healthy. Seven years on the list, and it was a long time. I have big lungs, and unfortunately, there weren't a lot of big lungs during those 7 years that managed to make it into the Midwest. Unfortunate for me, fortunate for everybody else that went to Cleveland. They all got transplants; I didn't.

But here's basically, you know, my whole concern and what I think about this particular device, some thoughts, if you will. COPD currently is the number three leading cause of death in the United States. Nothing new to you guys; you know these things. But what's the one way that you can help a COPD patient other than, you know, the typical management through drug therapy, physical therapy, rehabilitation? To transplant. And many of my friends in the Northeast have been on the list for many years unfortunately because the programs up there up until recently didn't have the opportunity to do as many transplants. Now, some of us were told that the donors just didn't exist; the programs were short of staff. Basically, what it all comes down to is there just weren't enough lungs, and those lungs that were out there ended up going someplace else in most cases.

So I guess my point that I'm trying to make here, in a very ineloquent way, is that if you have the opportunity to approve something that's going to extend the time between donor and transplant, I cannot see how, in all conscience, you could vote against it. It's as simple as that. The opportunity to increase lungs in the United States is a necessity at this point in time. Too many people and too many friends have died because the lungs just didn't come through, or the ones that did were horrendous, or the ones that did come through were on the East Coast and they're on the West Coast. They wouldn't survive the trip.

So that's my concern, and that's why I think, quite frankly, it's up to you guys. You people are the experts, and we're asking, as a group of patients, for you to seriously spend

hardcore time and really think about this decision. Think about your patients, think about your friends, your family. And God help you if you have COPD.

Thank you.

DR. SCHWAITZBERG: Thank you so much, Mr. Stoker.

Our next speaker is Charles Alexander.

MR. ALEXANDER: Thank you for the opportunity to present. I have no financial disclosures. And being local to this area, transportation as well was not provided.

I have had the opportunity in my career to be a transplant coordinator, the actual -- the folks who are on site during the procurement of donated organs. And later I had the opportunity to be the president of that national association, will be president of the Association of Organ Procurement Organizations, and also a past president of UNOS. So I've had an opportunity to touch different areas of how organ donation works and how organs are allocated.

I currently serve as CEO of the OPO here in Baltimore, just north of us, and each year we're providing 70 to 80 lungs for transplantation, and I'm very well aware of the wait list and the patients we just heard from today and the impact this kind of technology can have on them. We had a wait list of over 200-and-some people 5, 6, 7 years ago. We currently have 20 active patients on our local list because we've been able to explore technologies and other therapies to make more lungs available and get patients transplanted. This is a big part, ex vivo, this technology is a big part of the future of lung transplantation, and it's not because we're going to resuscitate lungs and we're going to do different things to them. What it's going to do is allow us to have the time to have donor lungs find appropriate waiting recipients. That is a very big part of what this technology allows us. There may be p-values and statistical significance and study design that, you know, can be questioned, but the reality is the clinical implications are real. Organs need to be able to be shared more

broadly in order for us to find appropriate recipients and to afford transplant teams the opportunity to have the time in the operating room to perform the surgery successfully.

The last thing I'd like to mention is expansion of the donor pool is a real thing. In some areas now, it's 20% or more of organ donors are recovered under DCD protocols, donation after cardiac death protocols. Up until just a few years ago, lungs were never transplanted or very, very rarely transplanted from this patient population. These kinds of technologies give us the opportunity to expand the donor pool. Twenty percent of all donors were for lungs to be recovered and transplanted today, and that's part of our possibilities and part of our future.

Thank you.

DR. SCHWAITZBERG: Thank you very much.

Our next speaker is Dr. Gregory Cosgrove.

DR. COSGROVE: Good afternoon. My name is Gregory Cosgrove. I have no financial conflicts. My travel was supported by TransMedics today.

I am the Chief Medical Officer of the Pulmonary Fibrosis Foundation and associate professor at National Jewish Health in Denver, Colorado. I've been working in an interstitial lung disease clinic there for the past 18 years, which happens to be the largest interstitial lung disease clinic in the world, caring for more than 5,000 patients a year.

So I'm speaking on behalf of those who I advocate for from the foundation but also as a pulmonologist that's utilizing this lifesaving technique, in terms of lung transplantation, to help the lives of those with a deadly disease. As we've heard earlier, pulmonary fibrosis can be rapidly progressive and takes the lives of those individuals and significantly impairs their quality of life while they're living with the disease. With a prevalence of greater than 200,000 for one disease, which is IPF, of the 180 different fibrotic diseases, it's quite clear this is a burden which will continue to persist in the United States and throughout the

world. Importantly, we know that based on the data today, perhaps 800 patients with IPF will be transplanted this year. That leaves approximately 42,000 individuals dying from that disease.

So what can we do to help those individuals? There are two approved, FDA-approved therapies for the treatment of pulmonary fibrosis, in particular IPF, which slows the progression of disease. It does not cure the disease, but it halts the progression. The one lifesaving therapy for those with pulmonary fibrosis is transplantation. Increasing utilization of lungs, as we've heard, is of paramount importance, not to do anything other than to save the lives of individuals.

So as I think about the patients that I care for, as I think about the individuals for whom I advocate throughout the United States and the colleagues throughout the United States that I represent as well, I would ask you to consider the benefits and the risks of the OCS system and, with that knowledge, understand the increased availability and utilization of those lungs that can be procured with this system not only helps those individuals and saves their lives with a transplant but also impacts the lives of many more: their family members, their friends, and other individuals across the world.

Thank you very much.

DR. SCHWAITZBERG: Thank you so much.

Our next speaker will be Dr. Michael Smith. And after him, if we could get Mr. Eidbo, Dr. Madsen, and our final speaker, Scott Johnson, all teed up and ready to go.

DR. SMITH: All right, thank you for the opportunity to speak on behalf of this very important technology today. My name is Michael Smith. I am a Professor of Surgery at Creighton University School of Medicine, Phoenix campus, and surgical director for the lung transplant program there. As Ms. Krushelniski mentioned earlier, we have a very busy lung transplant program that we help lead there, and I, fortunately, had the great opportunity to

train with the guys who did the first successful isolated lung transplants in the world back in the '80s with Alex Patterson and Joel Cooper when they were in St. Louis. And since that time back in the '80s, two things have not really changed in lung transplantation as compared to the other solid organs, like kidney and liver and heart. And, number one, the donor shortage is more profound, as many people have said here, for lung. And, number two, the long-term survival is substantially worse for lung transplantation.

For example, when we look at the overall donor population in the United States, we see that only 20% of donors are considered acceptable for a lung, and that means that 80% of potential donor lungs are never gifted to our recipients that are waiting, and sometimes dying, on the list.

Further, we know that when we try to be more aggressive with expanding the donor pool by taking lungs from extended criteria donors, the risk of life-threatening early lung allograft dysfunction, primary graft dysfunction problems, are much higher. And with regard to the long-term survival, we know that since the beginning of lung transplantation back 3 to 4 decades ago, that 5-year survival for lung transplant has only gotten marginally better than 50%. And that's in stark contrast to other solid organs such as kidney, liver, and heart. And, furthermore, when we look at those organs, we see that, you know, 5-year survival is 75 to 80% or so. What we also see is that, you know, recipients who were unfortunate enough to have this early lung allograft dysfunction but fortunate enough to recover, they have even worse long-term survival.

So it's really a catch-22 when we're trying to evaluate donors for these waiting recipients. And so the acceptance and advancement of the field of ex vivo lung perfusion has the potential to positively impact both of these major limitations to the field of lung transplantation. In fact, the data from the INSPIRE trial has already shown an impact on the incidence of primary graft dysfunction, even in standard criteria donors.

Indeed, as Ms. Krushelniski, our Vice President of Transplant Operations, pointed out that even in our own institution, we saw that the OCS Lung population had benefits in terms of their length of stay, time in the ICU, primary graft dysfunction, etc., that was very similar to what we saw in the whole trial. More time will be needed to see what is the extent of these short-term benefits and how they will affect long-term survival, so time will tell.

So we found this technology also in our hands to be --

DR. SCHWAITZBERG: Please conclude, Dr. Smith.

DR. SMITH: Will do -- to be safe and effective in the management of our donors. And, indeed, it does require more resources to implement, but we feel it's well worth the effort on behalf of our transplant recipients in the hospital.

Thank you.

DR. SCHWAITZBERG: Thank you very much.

Our next speaker will be Mr. Elling Eidbo.

MR. EIDBO: Good afternoon, ladies and gentlemen. Thank you for the opportunity to address you today. I have no financial disclosures to make.

I'm the CEO of the Association of Organ Procurement Organizations (AOPO), the association for representation of all 58 federally designated organ procurement organizations which serve the entire United States. I've served in this capacity for the past 6 years and have another 10 years experience working on the front lines of organ and tissue donation and recovery in hospital ICUs or with donor families, with donors, with recovery teams and transplant programs. I know well many of the critical challenges, the needs, the frustrations and the opportunities for this field of organ donation transplantation, many of which were noted by some of our previous speakers.

Ours is a mission of overcoming obstacles and constraints to save lives through organ donation and transplantation. Of the many constraints we face, several that stand

out for us, as mentioned here today, are logistical burdens, time, and organ function. Each of these overlap a bit but dramatically influence organ availability and utilization. That's organ availability and utilization. Failure to maximize organ availability, for us, results in death. Technologies that can significantly improve the availability and thus utilization of organs should be the top priority for us all, as the cost of failing to transplant are huge but the benefits of successful transplantation are much larger. Quite frankly, technology advancements are long overdue.

Perfusion-based preservation is not new to us. I can still remember 20 years ago putting kidneys on what we then called the pump, and only after being able to demonstrate, over a number of hours, the vascular resistance reduced to within the normal range, we would be able to have the transplant surgeons accept and successfully transplant the kidneys, successfully transplant those kidneys and more, at their patients' and their convenience. These kidneys otherwise would've been discarded. The benefits are crystal clear.

You've heard about the many numbers of organs discarded. For lungs and hearts, however, these numbers are understated, as is often the case with less-than-perfect organs. Without much better -- without better information about their function or the ability to overcome the logistical burdens, the time constraints, and organ function trends over time, they're not even recovered from the donor for transplant, and thus their numbers don't make it into the statistics for discarded organs.

The easiest example to illustrate logistics and time constraints are the organ procurement organizations that serve Puerto Rico, Alaska, and Hawaii, but there are many others. Three weeks ago just, I was talking with a CEO from Hawaii. They had a mid-20s male donor case with healthy heart and lungs. Those organs could have saved the lives of two people if they had this machine discussed today, or one like it. The distance or the

transport time was just too great.

As noted, perfusion technology platforms permit us to better mimic healthy physiologic conditions, allow the time window within which the organ must be transplanted to be significantly extended, and thus allow us --

DR. SCHWAITZBERG: Please conclude your comments.

MR. EIDBO: Yeah -- to transport them further distances to better schedule when transplant procedures take place and to better assess organ function over time. These are advantages and advancements that are simply not currently possible for organs such as hearts, lungs, and livers under the current model of the organ in a bag of ice or, as referred to here today, standard of care. I encourage and welcome you to approve these technologies so that we can surmount these constraints described and save more lives.

DR. SCHWAITZBERG: Thank you.

Our next speaker is -- is it Dr. Madsen or -- Dr. Madsen from -- another MGH person visiting from up north.

DR. MADSEN: Joren Madsen. I am a cardiac surgeon at Mass General Hospital. I am the Director of the MGH Transplant Center. I'm the Paul Russell Chair at Harvard Medical School, and I'm the first president to be elected to -- the first surgeon to be elected to the presidency of the American Transplant Society. I've had a lot of experience in transplantation, and I'm here for a request and a comment.

My request is simple, that as you pick apart the trial and you deal with p-values and decimal points, you remember the big picture. This is a revolutionary technology. It's going to change the face of transplantation; it already has in Europe. Remember that.

The second thing is a comment. As you evaluate the trial, you're also evaluating the dream of a single person who has committed his whole career to this, and he has developed something incredible. I think of it as the EVLP equivalent of the Macintosh computer. It's a

beautiful system, and it works very, very well. I ask you to let us use this to save lives, and I ask you that in the name of the patients who have been transplanted and who will be transplanted with these patients.

Thank you.

DR. SCHWAITZBERG: Thank you so much.

Our final speaker is going to be Scott Johnson.

MR. JOHNSON: Good afternoon. My name is Scott Johnson, and I am the first person in the Midwest to have the OCS Lung machine transplant. And I was diagnosed with severe COPD, emphysema, and I was asked if I wanted to be part of this study. I signed up without hesitation. I was told when I got put on, it could be quite a while before I had my transplant. It actually came out to be exactly 3½ months when I got transplanted. I spent only 1 day in ICU. I was in the hospital a total of 8 days. The ninth day I went home. My lung function has been steady and has actually increased, but it's never decreased below 80%. I've had no issues, no rejection, and I'm just here to ask you to approve the OCS Lung System because it makes the lungs available for people, and in my opinion, it will travel longer. So that's basically all I have to say.

Thank you.

DR. SCHWAITZBERG: Thank you very much, Mr. Johnson.

I'd like to thank all the members of the public. It is quite a commitment to come here and speak for anywhere from a minute and 8 seconds to 3 minutes and then get cut off by the Panel Chair after you've come such a long ways, but we wanted to be fair to everybody. And particularly I'd like to thank the patients for coming and sharing their stories.

At this time I'd like to entertain any questions from the panelists who have any specific questions for our open public speakers. Are there any questions from the Panel?

(No response.)

DR. SCHWAITZBERG: Okay. I now pronounce the Open Public Hearing to be officially closed. We will proceed with today's agenda. We will now begin with the Panel deliberations. Although this portion is open to the public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who do speak identify themselves, including the panelists, to make it easy for the transcriptionist.

At this time we would ask the panelists that asked both the FDA and the Sponsor to prepare some questions, if you were a panelist and had a homework question for the FDA or the Sponsor and want to go first, please raise your hand. For questions that were unanswered at the time of presentation.

Dr. Connor.

DR. CONNER: Sure. Yeah, I requested a specific plot, in particular, asking whether the PG3 or PGD3's had poorer outcomes, whether you were -- you know, didn't have any event, whether it was just at zero or later.

DR. HASSANEIN: Mr. Chairman, can I -- Waleed Hassanein from TransMedics.

Dr. Connor, we are working hard trying to get that analysis. Unfortunately, we have not completed that analysis. However, we have PGD3 at T0 and PGD3 within the first 72 hours correlation to BOS-free survival over the 2-year period in INSPIRE. If these would be helpful, we'd be happy to share them with you.

DR. CONNER: Okay, let's see it.

DR. HASSANEIN: So this is PGD3 at T0 compared to BOS-free survival, incidence of BOS-free survival stratified by PGD3 at T0.

DR. CONNER: Okay. Well, no, I don't think we need to spend time on that.

DR. HASSANEIN: Okay.

DR. CONNER: Thanks.

DR. SCHWAITZBERG: While you're at the podium, you now have the opportunity to correct any misstatements, any questions, any clarifications that you have. I will give you the floor for the next 5 minutes if there are any burning issues that you wish to address to the Panel.

DR. HASSANEIN: Thank you, Mr. Chairman. There was quite a few. First, let me address Dr. van Berkel, related to the discrepancy between the TransMedics' and the FDA's graphs. We checked our graphs; our graphs is based on the statistical test. There's no error in our graphs for the specific slide you highlighted.

Next, I would like to bring Professor Van Raemdonck to specifically address some of the statements made on PGD.

DR. VAN RAEMDONCK: Thank you. Dirk Van Raemdonck.

I appreciate the time that Dr. Sapirstein has put into the interpretation of the PGD 2005 and 2016 consensus statements. However, I would like to clarify two points as the Co-Chair of the ISHLT PGD working group.

Number one: Yes, it was not clear whether we should interpret this for extubated versus intubated patients. However, if you look at this slide, there is indeed a contradiction in our favor because, if you look at the caveat, it said absence of any radiological infiltrate should be PGD 0, and here in this table, we say it should be greater than 300 mm. So there is a contradiction.

Number two: Dr. Sapirstein has projected the text coming from the 2016 paper, and he has claimed that this paper is in press. However, it's not in press; it's on my computer here in my bag. So this paper is still in the process of being submitted to the *Journal of Heart and Lung Transplantation*, so I do not know where he gets these texts. And the T0 is still kept in the 2016 definition.

And, finally, I think it's important that we keep the PGD grading in our further studies that we want to do in our postmarket approval studies.

Thank you.

DR. HASSANEIN: Mr. Chairman, if you'll allow me, please, can I ask Dr. Abbas Ardehali to specifically address the issue of logistic screen failure and the overall screen failures and impact on donor and recipient demographics?

DR. ARDEHALI: Abbas Ardehali from UCLA.

As I'm sure everyone has realized throughout the morning and early afternoon, that the transplantation, specifically lung transplantation and organ allocation, is a complex process. And as I said this morning, we fully acknowledge the fact that there is an imbalance in the screen failures between the two arms. However, I want to take a few seconds to just go over the process and how the screen failures occurred.

As you well know, once a recipient has been randomized to either the OCS or the control, and a suitable donor has been identified, a tentative donor has been identified, we send a team out. The team goes out to the donor hospital, looks at the donor organ, and at that time makes a decision. Most of the time, that decision is based on the inclusion and exclusion criteria that were predefined. At the donor hospital, that decision is made by the transplant team, not the medical adjudicator, not the sponsor, and before the transplant has occurred, without a knowledge of what would be the outcome of that specific recipient.

So to think that the screen failures would introduce a bias just because the team, based on their inclusion and exclusion criteria, excluded a donor, it seems to be pushing the discussion a bit too far. So I hope that you agree with me that the decision regarding the screen failures were made *a priori* before an organ was deemed eligible and harvested without knowledge of what the recipient's outcome will be.

Having said all of that, I also want to make sure that we review the donor

characteristics. The donor characteristics give me assurance that the quality of the organs that went into our recipients in the control arm and the OCS arm were nearly identical.

DR. SCHWAITZBERG: You've made that point very clearly before. Let's move on.

DR. ARDEHALI: Thank you.

DR. HASSANEIN: Mr. Chairman, may I answer one more question?

Dr. Meyer, you asked about -- I believe Dr. Meyer or Dr. Moon asked about the in-hospital mortality window. We followed all those patients during hospitalization. The farthest out was 151 days that was on the vent throughout the time. And Dr. Gregor Warnecke can address that specific patient.

Next, the question -- there was another question from Dr. Nathan related to baseline of FEV1. May I ask Dr. Warnecke to address that question?

DR. WARNECKE: Yeah. So this slide shows --

DR. SCHWAITZBERG: Remember to introduce yourself.

DR. WARNECKE: Yeah, I'm Gregor Warnecke from Hannover Medical School.

So this slide addresses the question, what is the lung functions measured by FEV1% predicted in both study arms? And although it's not showing the best FEV1 specifically, we can assume that the 12-month FEV1% predicted is close to the best FEV1 measured in the individual patients, and it clearly shows that the OCS group is as good or better as the control group at 24 months here and similar at 12 months.

Thank you.

DR. HASSANEIN: There was also a question related to the use of cardiopulmonary bypass after transplant as a potential -- that was described in the FDA presentation as a potential confounding variable to the PGD at T0. May I ask Dr. Gregor Warnecke, please, to comment on that based on the recipient characteristics?

DR. WARNECKE: Yes, we have the data for use of extracorporeal circulation during

the lung transplant procedure, and it shows it was 38 -- the incidence was 38% in the control and 40% in the OCS arm. We don't have data on the emergency use of extracorporeal circulation, but it shows that the rate of use of ECC is at least as high in the OCS arm. So that cannot account for the difference in PGD3 at T0.

DR. HASSANEIN: The next question was from Mr. Naftali related to chemical benefit in patients with reduced PGD3 within the INSPIRE trial. I would like to ask Dr. Gregor Warnecke to comment on that.

DR. WARNECKE: This is just to show additional post hoc data on potential clinical benefits in the trial, and this shows that patients with PGD3 within 72 hours have a clear association with long hospital and intensive care unit stays and also with altered incidents of bronchiolitis obliterans in the trial. So we assumed that there should be clinical benefits of reducing PGD3 within 72 hours.

DR. HASSANEIN: Mr. Chairman, the last question, I believe, was Dr. Moon asked about how many PGD3's were graded where ECMO was used non-prophylactically, just ECMO. The number was a total of seven in the OCS and two in the control group that were graded PGD3.

DR. SCHWAITZBERG: Excellent. While we have you, I'd like to ask the question that we glossed over pretty quickly, of the OCS solution versus the other solution. Did you agree that they were chemically equivalent, and if so, is there like some special sauce? You don't have to give away your trade secrets.

DR. HASSANEIN: No, no, no.

DR. SCHWAITZBERG: But given the chemical equivalency, I'm just a little mystified at the difference in the outcomes. Can you explain that?

DR. HASSANEIN: Sure. Thank you for the question. Initially, we believed that they're chemically equivalent. However, the clinical comments we received that we shared

with FDA led us to -- based on the analysis of the solution versus the LPD solution, we saw that the outcomes were different. We can't comment on where that difference is coming from. The only signal that we have, given that we're not the manufacturer and we do not control the manufacturing of the LPD solution, we control the manufacturing and the biocompatibility for our solution, is we find that our solution is packaged in an inert biocompatible bag. The other solution is packaged in a different packaging material. Could that have attributed? Maybe. We cannot comment. We want to focus on our solution that we're here kindly asking the Panel to consider for approval. So that's the only limitation -- the only thing that we can comment on, on the two different solutions.

DR. SCHWAITZBERG: Dr. Fisher.

DR. FISHER: I would just like to add that if we do need to go over the chemical equivalence, we have an analytical chemist here who's happy to do that, and we have requested from the company information to give us something that shows that there could be something affiliated with the containers or something, that the company has not been forthcoming with that information.

Thank you.

DR. HASSANEIN: May I clarify that, Dr. Fisher? The company provided all the data that the company was able to achieve. We provided biochemical testing, looking at trace elements of plasticizers, and we, in fact, found some trace elements. But we're limited to the amount of data that we can generate, given that we're not the manufacturer of the LPD solution and we were prohibited from acquiring additional material to even test it further. We shared all the data that TransMedics had with the FDA, and we clarified the issue of the lack of access to that solution any further, given that we're not the manufacturer and we provided all of that in our PMA, through our PMA discussion. We have no additional data. Let me be clear, we have no additional --

DR. SCHWAITZBERG: You made that point.

DR. HASSANEIN: Yeah.

DR. SCHWAITZBERG: Did you have further questions? While we have the Sponsor at the podium, do any of the panelists have additional questions? Why don't we start with Dr. Afifi.

DR. AFIFI: I have a statistical question. There was an interim analysis done, but no adjustment of the significance level was made. Can you explain why this was not done?

DR. HASSANEIN: Sure. May I ask Chris Mullin to address this statistical question?

MR. MULLIN: Chris Mullin, biostatistician.

So you're right, I think it's an important point that FDA raised. We tried to be very clear on that, that it was not done. Those interim adjustments, by necessity, really need to be pre-specified. And so such an adjustment wasn't done as part of the study.

DR. AFIFI: Okay, another question. The clinical centers were not blinded and we've heard why that was done from your point of view. Were the outcome data available to the Sponsor on an ongoing basis or at certain intervals prior to the request for the change of the criterion?

DR. HASSANEIN: The study was an open-label study. We have access to the data. We are required to provide an annual report to FDA every year on all the safety profile of the data, the subjects enrolled, and any other clinically relevant matters. So, yes, our clinical operations group had access to that data, and we provided updates to the FDA on an annualized basis.

DR. AFIFI: And was the request of the change, then, in the criterion made on the basis of some of these analyses?

DR. HASSANEIN: If you allow me to make a comment, and then I will address the question directly. We recognize how unusual this situation is. We acknowledge it, we've

learned from it, we initiated four additional studies after INSPIRE, and this situation never -- and will never happen again. This unfortunate situation was primarily an outcome -- to answer your question directly, it was primarily an outcome of the very complex and very prolonged regulatory history that pushed us to agree to something that is completely different from the original clinical design of the study, that we worked very hard with the clinical leaders in the field to come up with an appropriate outcome measure that would be appropriate to assess effectiveness of a preservation technology designed for minimization of ischemia. That was the driver.

The published data and then finally the time distance between the first patient in the U.S. and the appeal -- and the amendment was primarily driven by similar negotiations on a separate trial, that we had to elevate it to an appeal process. It's unfortunate. We learned from this. It never happened again, and it will never happen again. Unfortunately, we're here looking at this 6 years later, 4 years later, and we recognize that, and from TransMedics' side, this will never happen again, and we will find a way to reach a consensus and not allow the time to elapse that long. Again, on behalf of TransMedics and the investigators, we recognize it is very unusual, and we've learned from this experience.

DR. SCHWAITZBERG: Dr. Yuh.

DR. YUH: It goes beyond unusual. And I'm not sure I get the thrust of your answer. I guess the critical question is did you have access to interim analysis of the data prior to changing your definition of the primary effectiveness endpoint, and did that influence that? Because that's what's kind of hanging around, you know.

DR. HASSANEIN: Sure.

DR. YUH: That's what's raising that --

DR. HASSANEIN: Right.

DR. YUH: -- in spite of the fact the FDA advised you not to change it.

DR. HASSANEIN: Sure. So, Dr. Yuh, we completely agree. This is exactly the insinuation; this is exactly what's hanging around. We did not change our endpoint because of looking at the data. But I'm not going to stand here and say that we didn't look at the data, because the data was available, okay? I want to be very clear; the data access had no relevance in our view. We understand it's unusual, and I'll explain why. The data that the FDA used in their presentation was presented by Dr. Warnecke because he was invited, as the lead investigator, to present an update on the trial for the ISHLT. It was presented as unadjudicated and unmonitored data and was presented as such.

However, we understand it's unusual. Our position on the amendment was primarily driven to harmonize the trial to the original clinical design, and I would like to comment -- ask one of the two co-principal investigators to comment from their perspective as well because they were involved in helping us come up with the right endpoint that would assess the --

DR. SCHWAITZBERG: I'd like to hold off bringing them up because I'd like to get an answer to his question because I don't think you've answered --

DR. FISHER: Thank you.

DR. SCHWAITZBERG: -- the question that is hanging out there as the white elephant in the room. There are four conditions. Three of them don't support non-inferiority. One of them, which was not in the original trial design, does and you have to come up with a better reason than saying we want to go back to our roots of the original study that we designed before it was submitted to the FDA because this is really -- I can just sense it in the room -- this is an issue that's driving the Panel members.

So, Dr. Connor, if you want to elaborate.

DR. CONNER: So let me frame this exact question in a different way. You saw the data, we know you saw the data, and you acknowledge that, and that's totally appropriate

and that was by design. If the primary endpoint had been looking great, would you have bothered to appeal to the Office of the Director?

DR. HASSANEIN: Absolutely.

DR. CONNER: If your data were looking great, you had published interim data and it was still looking fantastic and you were hitting the primary, you would nevertheless have gone through the problem of appealing, which risks offending your review group, you would've appealed anyway because you so philosophically believed that including a transient zero for someone who is now alive and well is equivalent utility of a patient who died at 15 days?

DR. HASSANEIN: Absolutely.

DR. CONNER: Okay.

DR. HASSANEIN: Absolutely. And this is why, Mr. Chairman, this is why I wanted to ask one of the co-principal investigators to address that question because the data that was presented by FDA -- actually the OCS was doing well in every time point. However, we did not believe that assessing PGD at T72 is really directly related or even remotely related to the -- or less related to the preservation technology. That is really what drove the process.

DR. CONNER: Okay. No, that's fine. So my question keeps going back to, then, the differences in the zeroes, not in the 24s, not in the 48s, that I would love to see data that says zero is a transient zero, it actually affects long-term outcomes. And that's what I asked to see. I mean, we saw three patients here today, and I'm so thankful that you're able to be here and support this today. Were any of those transient zeroes? There's actually a pretty good chance that one of those three were, given how many transient zeroes there were that then went away. Chances are they are and they're treated as failures, even though they're here and thankfully doing very well.

DR. HASSANEIN: I don't know the answer to that question. I don't know the answer

to were they transient zeroes or not.

DR. SCHWAITZBERG: So pick one of the two, and if we can try to get some sunlight rather than repeating the same thing over and over again, if you have some insight, because I don't think the panelists are completely convinced that if the trial had been going well, that you would have petitioned the FDA to change your endpoints. And I'm just reading the thermometer and looking at the faces. So I'm trying to give you every opportunity to persuade people that you would have changed a successful trial because of some willingness to go back to a philosophic viewpoint. So the floor is yours. Remember to introduce yourself.

DR. ARDEHALI: Abbas Ardehali from UCLA.

Thank you for the opportunity. This is the slide that was presented at ISHLT. It was based on 90 patients. The rationale for changing the endpoint was not based on this, in my opinion, but based on the following slide that I will share with you, showing three studies showing that the PGD3 at Time 0 makes a difference in the recipient outcomes. The first panel on the left, this is a study from Whitson et al. from 2007. The following study was done by the group from St. Louis. And, lastly, the group from UCLA has shown that patients -- transient PGD3 at Time 0 makes a difference in patient outcomes. I had access to that data before the study was published in the *AJT,* and based on that information, as a part of the steering committee, it was my opinion that it should change.

Thank you.

DR. SCHWAITZBERG: Well, while you're up there -- excuse me, stay up there for a second. If that's the case, why didn't you petition the FDA to change the endpoint from PGD3 to just Time 0, if it's that important?

DR. ARDEHALI: Well, PGD3 at Time 0 is not the sole point that we're interested in because I think PGD3 at T72 is also important, probably more important than at Time 0.

However, if I have access or if I have a patient that has PGD3 at Time 0, I would not consider that patient would have as good of an outcome as somebody who had PGD 0.

DR. SCHWAITZBERG: But because you said it might be more important in that group, that non-inferiority was not statistically significant. So I'm trying to put the two statements together in my own head, and you know, I don't vote unless there's a tie.

DR. ARDEHALI: In my opinion, PGD3 matters at all times. PGD3 is important probably more at 72 than at Time 0. But as a clinician, I would not ignore PGD3 at Time 0.

DR. SCHWAITZBERG: Thank you.

Other panelists with questions? Dr. Yusen? Dr. Moon?

DR. YUSEN: No questions.

DR. MOON: I've got a question about the protocol violation patients. It seems to me these protocol violations were determined after we already knew the outcome of the patient. Is that true?

DR. HASSANEIN: If you allow me to address that question in two pieces.

DR. SCHWAITZBERG: Can we start with a yes or no?

DR. HASSANEIN: I don't know which specific protocol violations. Most of the protocol violations -- not most, all protocol violations in our CRFs were determined by the site, by the principal investigator, and then it was captured by our monitoring team and then went through the data cleanup and adjudication process. So every protocol violation in there has data in the CRF indicating that the patient did not meet the eligibility criteria for one of the variety of reasons.

The other point I wanted to mention, specifically related to all the specific patients that were highlighted in FDA's presentation -- two points. The INSPIRE trial succeeded in -- had a successful BIMO audit for 9 days with every single screen failure and every single protocol violation highlighted today in our presentation and FDA's presentation. It was

looked upon by a trained BIMO auditor, and nothing was found to suggest any trial misconduct.

Number two, the patients that were highlighted today, I'm happy to go over every single patient that Dr. Sapirstein addressed or discussed. There's additional information that were not shared with the Panel. That specific patient where the question about randomization, that patient was never randomized. The retrieval team went out and did not even know that that patient was in the study. The next morning, the research coordinator showed up and said, oh, that patient was consented for the study, and that's why that patient did not follow the protocol definition of randomization. That's why that specific case. So there are other sides to the story. The bottom line is this study has gone through extensive BIMO review for 9 days, and no issues of study conduct was highlighted.

DR. SCHWAITZBERG: But you still didn't answer his question. His question was, were the protocol violations adjudicated at a time when the outcomes were known? Is there anybody on your team who can --

DR. HASSANEIN: Yes.

DR. SCHWAITZBERG: -- specifically answer yes or no to his question?

DR. HASSANEIN: May I ask Dr. Khayal to address that point?

DR. SCHWAITZBERG: I'm just trying to make sure the panelists' questions are answered.

DR. KHAYAL: So protocol violations, as Waleed mentioned, were entered by the sites in the CRFs and note files that were documented and signed by the PI. Based on this documentation, this was all provided to the medical monitor for further assessment and final assessment of each of those protocol violations. So the initial assignment is done by the site and the PI. The Sponsor's responsibility is to provide all this documentation to the medical monitor, then, for final adjudication. So this process happens and is ongoing

throughout the conduct of the trial, and yes, the outcomes are unblinded, as we've been mentioning, so we know the outcomes as they come across. But this doesn't influence the direction and the process that's followed consistently throughout the conduct of a trial.

DR. SCHWAITZBERG: Dr. Moon, did he answer your question?

DR. MOON: Well, I'm not worried about the randomization patient. I'm worried about the five patients at the bottom of this graph, that one was ABG time stamp; one was the power source going out in the helicopter, which is going to happen in the future; the bullae that was determined later and the two active pneumonias that were determined post hoc compared to the one active pneumonia that was determined in the SOC group, because if all five of these had PGD and only the one had PGD in the SOC group, that changes the statistics.

DR. HASSANEIN: Sure. To address specifically the patient with the pneumonia, can I have the slide for the patient with the pneumonia, please? Those two specific patients, we looked into them in detail. That patient that was excluded had several -- the patient that was excluded from the study is in the top panel. As you can see, the multiple forms that shows what's going on with this lung is highlighted. In the eligibility donor form, the center entered data identifying that patient of presence of active pulmonary disease. The site also entered data in the donor assessment form as pulmonary edema, possibly due to aspiration, ongoing left lower lobe consolidation, collapse in focal areas of left upper lobe, pneumonic infiltrate. In the third form, the site entered data -- mucopurulent secretions, apical lung scarring.

The FDA control subjects that were highlighted, that was transplanted at the same site, we believe that the highlights there are upper respiratory flora. That's why it was not captured; it was not entered as ineligible. You see the difference between the eligibility form that the site entered versus the one on the bottom; that's the difference. Every site

enters this data. We didn't qualify these patients as protocol violations. The site has to enter the data in the protocol eligibility form. That's what we're trying to highlight.

DR. SCHWAITZBERG: Thank you.

Dr. Fisher, you had a comment?

DR. FISHER: I actually had a question that I was trying to get more information for. It had to do with the in-hospital time and how that compared to between groups and how long it went.

DR. HASSANEIN: Sure. Can I ask Dr. Warnecke to address that question? In-hospital mortality. Dr. Fisher, you referred to in-hospital mortality?

DR. FISHER: You extended the 30-day survival time --

DR. HASSANEIN: Mortality.

DR. FISHER: -- to include something called in-hospital time.

DR. WARNECKE: So, yeah, overall in-hospital time for the entire study population, as shown in the core presentation -- Gregor Warnecke from Hannover, sorry. And that was shorter in the OCS arm than in the control arm. With regard to in-hospital mortality, so in-hospital mortality is the more appropriate way of measuring mortality after lung transplantation. The only substitute for that would be 1-year mortality. Thirty-day mortality is clearly inferior, and I don't think there is any in-consensus in the scientific field about that notion today. So in-hospital mortality really is the important way of looking at this, and the patient with the longest time from transplantation until death in-hospital is a patient who stayed in hospital for 151 -- that's coming up? And this was for in-hospital for 151 days, and that's a control group patient. This patient was on ventilator for the entire 151 days. He was on orotracheal tube for 12 days, then tracheostomies and tracheostomy for the remainder of the 151 days, and then died of secondary complications of this prolonged intensive care unit stay. And that's typical for lung transplantation with patients

with failed lung grafts.

DR. HASSANEIN: Mr. Chairman, if you'll allow me.

Dr. Connor, I just got data; they're trying to graph it. With your permission, with your permission --

DR. SCHWAITZBERG: I'll give you a moment just before we go to the break to put your slide up. The one last question before we switch to the FDA comments is I would personally agree that in-hospital mortality is very important, and given the fact that you were changing other endpoints based on principles of good care and good science, did you request the FDA to change the mortality primary endpoint from 30 days? And if you didn't, why not?

DR. HASSANEIN: Because it's already in the protocol.

DR. SCHWAITZBERG: But the other things are already in the protocol, too.

DR. HASSANEIN: Right, but we -- again, we recognize the, we recognize the situation, and we wanted to minimize the changes to the core clinical principles that matched the original protocol design. The in-hospital mortality is already in the protocol. The others that were not in the protocol were completely removed with the initial approval.

DR. SCHWAITZBERG: We'll come back to your graph at the end of -- just before the break.

Dr. Fu, you or your team, would you like to make any clarifying statements, correct any misstatements, answer any questions for the Panel? Obviously, you should have an opportunity to do so. We will end at 2:45 on the break so we can keep the Panel moving. So I'm going to give the Sponsor just 5 minutes, so you can have about 15 minutes to make any other statements that you'd like to make.

DR. SAPIRSTEIN: Yes. In no particular order, I'll just make a couple comments. First, about the question of interim looks and the effect that we perhaps thought it might have

had on the Sponsor's analyses. We weren't trying to say the ISHLT 2013 presentation or the subsequent 2014, that those per se were the impetus for the Sponsor to change the endpoints. We were using those only to illustrate that the Sponsor had iterative and repetitive access to endpoint data, both at that time and before, to the ongoing results in the study. I wasn't trying to imply that the investigators were providing impetus themselves for the change.

Regarding the ISHLT 2016 update, the question was where did we get that, and we were in press. We had discussions with other members of the ISHLT consensus group, and they affirmed to us that this was the final draft document that would be going to press, so my apologies if it's not in press at this point. I wasn't trying to dissemble that.

Oh, I guess there had been a question, I believe, from Dr. Moon about the differences in our Slide 67, which I believe was the endpoints, compared to the Sponsor's data; is that correct?

DR. MOON: No, I found it.

DR. SAPIRSTEIN: Okay, I'm sorry.

DR. MOON: I was looking at Slide 70 on your set, which was Slide 111, which is protocol violation -- one of the protocol violations. Which one?

DR. SAPIRSTEIN: Well, with the protocol violations --

DR. MOON: C. The one that didn't have the blood gas done in time and died, and then 2 years later they threw the patient out of the study.

DR. SAPIRSTEIN: Yeah. Well, about that, because I believe the Sponsor just discussed that particular patient in general, one thing I pointed out was some of that information, we saw that information that the Sponsor just presented right now about that particular patient, and I'm not trying in any way to turn this into such a granular-level discussion of individual patients. We recognize this is a large study, and we want to look at

the totality of the data with that patient themselves. So I think some of the information that was put up on the slide perhaps might be a little bit confusing because those were earlier assessments of that particular patient, in terms of upper -- I believe it was upper lobe consolidation. And, in fact, we went out of our way to actually speak with the investigator himself to say was this pneumonia, and we were told no, in his opinion as the transplant surgeon, it wasn't pneumonia. So I just wanted to clarify that a little bit.

DR. SCHWAITZBERG: Is the statistical discrepancy question answered to your satisfaction, Dr. O'Connor?

DR. O'CONNOR: Dr. Sapirstein, you know, somebody else on the Panel -- and I can't remember who had a question about your table of statistical significance versus the Sponsor's.

DR. SAPIRSTEIN: Okay, was that that table where I said --

DR. O'CONNOR: Yeah, I would like --

DR. SAPIRSTEIN: -- the four different -- yeah. It may not have shown up particularly well. Those were not the p-values. Those were the success-specific point -- the upper confidence bound of the differences in the treatment effects, which is the criterion by which the comparison to the non-inferiority margin was made. So that was probably the difference between our representation of it and the Sponsor's.

DR. VAN BERKEL: So, I'm sorry, I'm Victor van Berkel. I'm the one who asked that question initially.

So looking at your slides, your upper confidence interval using the PGD within 72 hours, admittedly the one that you guys think is less appropriate, but within 72 hours your upper confidence interval for the intention to treat was 11.8%. Looking at that same data on the Sponsor's slides, the upper confidence interval was less than 10%; it ended up being around 8, which is above -- you know, which crossed, of course, the 4% non-inferiority

threshold but was still just a different value. And presumably that's the same data.

DR. SAPIRSTEIN: Presumably it is. I'll defer to Ms. Liu to see. Those data were gotten from the PMA submission, those particular values, so I can't quite comment why there is a difference on the actual number.

DR. VAN BERKEL: Okay.

DR. SCHWAITZBERG: Since we were talking about criticisms of the trial, including over-enrollment at one of the sites, screen failures due to logistical problems that were more common in the non-U.S. sites, and given the fact that you've done a fair amount of reanalysis, did you do any analysis for site-specific biases? You know, is all of the protocol variations due predominantly to one site mis-performing? Did they have the best outcomes? Did you do any of those types of analyses as you were trying to understand the protocol violations?

DR. SAPIRSTEIN: We did. We did do those analyses, and I'll let Ms. Liu talk a little bit more about this. We did a pool, though, of the analyses and get -- and I'll let her get into the details of it. There was an interaction effect about different sites and particularly with United States versus outside United States. We didn't present that because, given the lack of statistical significance on the primary or the principal analyses, we didn't think it was appropriate to bring that up. But we did see a difference in the results between the United States and the outside United States sites.

Sherry, do you want to --

MS. LIU: So we did do poolability of the analyses for looking at each of the sites and then also U.S. versus OUS. There wasn't significant interaction between treatment versus the region, so we didn't -- but the estimates for the U.S. versus OUS is different. The OUS had better results compared to U.S. results. And we also saw an interaction between gender versus treatment, and the female actually had better results compared to the male.

DR. SCHWAITZBERG: So if we could summarize, the OUS, outside of the U.S. had better results and more screening failures?

MS. LIU: Yes.

DR. SCHWAITZBERG: Which you feel introduces bias, based on your previous presentation?

MS. LIU: Yes.

DR. SCHWAITZBERG: Your team.

MS. LIU: Um-hum.

DR. SCHWAITZBERG: Questions related to this?

DR. YUSEN: Can I follow up on that?

DR. SCHWAITZBERG: Absolutely. Turn your light on.

DR. YUSEN: I lost my train of thought.

(Laughter.)

DR. CONNOR: Yeah, a point I was having or thinking throughout, you know, the Sponsor, we kept seeing also the just better perfusate levels as well in that third plot, and I wondered if you or they had even -- and I don't know that you need to show this, but think about it during your continued review, is thinking about patients who were excluded because only the other -- the competitor's perfusate was available, whether they also then excluded the patients in the control group during that same time period because it sounded like there were only particular sites who didn't have access to the Sponsor's solution. So given it sounds like there isn't, you know, slight differences, now that means they're only throwing -- or excluding patients in one of the two groups, where they really should also be excluding patients in the control group who didn't have the OCS perfusate available at that time.

DR. SAPIRSTEIN: I'll just point out that actually they did, if you saw in the protocol

violations. Not screen failures, protocol violations. There were three control arms that were excluded from the per-protocol because they used the non-OCS, non-Perfadex solution, which was Celsior. So they did address that.

DR. CONNOR: Okay, yeah. And I was thinking, you know, there were times when they showed control, treatment, and then treatment with just their own perfusate plots, and really when they update to just that, there should be an analogous new control as well.

DR. SAPIRSTEIN: Yeah --

DR. CONNOR: That's what I just --

DR. SAPIRSTEIN: I understand what you're saying.

DR. YUSEN: Sorry. To follow up, I was distracted. In terms of the interaction, test for interaction, did we see or is there available a forest plot for test for interaction?

MS. LIU: No, we did not perform that.

DR. YUSEN: And the Sponsor did not provide that as well?

MS. LIU: No, they didn't provide any tests for poolability. We actually did that for ourselves.

DR. SCHWAITZBERG: Dr. Afifi.

DR. AFIFI: Yes. In your presentations, you talked about the potential for selection bias, and there are two sources, possible sources for that. One of them are the screening failures, and the other are the protocol violations. As far as protocol violations, we know that it made a difference because, when you go from the modified intention-to-treat to the per-protocol analysis, the results are different. The mITT is not significant, whereas the per-protocol is significant. The other, namely, the imbalance in screening failures, would be very difficult to assess the degree and the direction of bias. Do you have any thoughts, any more thoughts on that than you already expressed?

DR. SAPIRSTEIN: Well, I think we would agree with you completely, which is at the

foundation of our concern with this, is because there is a substantial number of patients for whom we don't have the data. You know, not so much in the statistical term, but those are missing data when we tried to do an analysis. We did try, and I showed that what we thought would be a somewhat acceptable post hoc sensitivity analysis of looking at the patients who had -- talking about the screen failures here -- had the off-study transplant with the assigned lung. We did that sensitivity analysis, and our inference from that sensitivity analysis was that the assessment of not showing non-inferiority was fairly robust, even when one does what we think was a fairly conservative approach to addressing the missing data. It was that 18 patients compared to zero patients to make that inference of no non-inferiority switch to non-inferiority.

DR. SCHWAITZBERG: A technical question, and then I'm going to instruct the Sponsor for his final comments for this session.

DR. HAMMON: Okay, could I give this question to one of the clinicians, either the surgeon from Germany or one other? No volunteers? This is not going to be a cross-examination.

(Laughter.)

DR. HAMMON: In looking at the graphs here, I notice that warm ischemia time, which is always the bane of the transplant surgeon, is increased for the second lung in the OCS group. So the first lung in the OCS group, 2.6 hours; 4.2 hours for the second lung. What's the reason for that? Is that because you only had one surgeon removing one lung at a time? Is it because you take the lungs back to the machine on a jet and that's how long it takes to get them there and you then have to hook them up? I'd like to know because in our group we have three transplant centers in North Carolina, USA, and we have all of our centers cooperate, and at our center we don't do lung transplants but we remove lungs for transplant, and we always try to take the lungs out simultaneously so that there is not an

increased warm ischemia time for that second lung.

DR. ARDEHALI: Abbas Ardehali from UCLA.

That's a very good observation. The fact of the matter is that when the lungs arrived at the implanting center, the lungs were taken off the device so that you could implant the first one followed by the second one. There is a theory that if we keep the second lung on the device while the first lung was being implanted, we could potentially decrease the cold ischemia time on the second lung and that, in fact, is in the process of being codified and implemented.

DR. HAMMON: I think you misunderstood me. What I'm talking about is what you have down here as total ischemia time, and if you have the lung on a device, then that's not part of that time; is that correct?

DR. ARDEHALI: Can I have that slide back again? This is the slide that you're referring to?

DR. HAMMON: Slide 60.

DR. ARDEHALI: CO-60?

DR. HAMMON: Yeah.

DR. ARDEHALI: Correct.

DR. HAMMON: Okay. So what you just said, then, didn't really count in that. So if you send -- go get two lungs from a single patient, do you take two devices with you?

DR. ARDEHALI: No.

DR. HAMMON: Just one?

DR. ARDEHALI: Just one.

DR. HAMMON: Okay, what happens to the second lung?

DR. ARDEHALI: The second lung sits -- as soon as the first lung or as soon as the organ arrives in the transplant center, it's taken off the device.

DR. HAMMON: Okay.

DR. ARDEHALI: Am I making -- am I not --

DR. HAMMON: I don't understand, unless you have both lungs hooked up to one device; is that what you're saying?

DR. ARDEHALI: That's correct. That's the double-lung block.

DR. HAMMON: Okay.

DR. ARDEHALI: It comes on the same device, and it's taken off. The first lung gets implanted --

DR. HAMMON: Um-hum.

DR. ARDEHALI: -- and the second one sits on ice --

DR. HAMMON: Right.

DR. ARDEHALI: -- until the team is ready for the second lung.

DR. HAMMON: So there is a period of time there when it's not on the machine?

DR. ARDEHALI: Correct, there's a time that is not on the machine. And as I mentioned, there is a process in place so that we can maintain the second lung on the device. That was not part of the study.

DR. HAMMON: Okay. Well, I guess my advice would be to decrease that warm ischemia time in the second lung by doing something different, and there are lots of choices there, but because there is a real chance of more ischemia and --

DR. ARDEHALI: Sure.

DR. HAMMON: -- bronchiolitis for that extra hour and -- 1.2 hours in there, okay?

DR. ARDEHALI: I just want to clarify that the second lung is not subject to warm ischemia; it's cold.

DR. SCHWAITZBERG: All right, those are technical questions. It's got to be a quick one.

DR. NATHAN: It was for Dr. Ardehali while he's up there. I'm looking back at the protocol and the patients who got randomized when the lungs became available and the metric for patients -- and I think you can argue about PGD and what's PGD and different grades, but the metric that's most important for patients is survival, and arguably not survival from the time of transplant but the survival from the time of listing. And was there consideration to randomizing patients at the time of listing? Where I'm going with this is if you knew that they were randomized to the OCS system, do you think you would've been more aggressive going out to get lungs for them?

DR. ARDEHALI: Abbas Ardehali from UCLA.

I think that that is a very reasonable hypothesis, but I cannot prove one way or the other. All I can tell you is that we randomized once a recipient had consented and a donor had become available. And the final adjudication, the final acceptance had to occur at the donor hospital once we were assured that that donor met the inclusion criteria and was harvested for that recipient. If none of that had happened, that recipient would either get that same lung outside of the study -- because many of the transplant centers that were part of the study were very aggressive centers. So if the donor is 66 years of age, we used those lungs, as you do. So we would use that lung outside of the study, and then it would be called a screen failure. But, in reality, what has happened was that we had specific inclusion criteria that we had to comply with, and for the integrity of the study, we had to follow those inclusion and exclusion criteria.

DR. SCHWAITZBERG: That's a great point. I'd like to ask Dr. Hassanein to come up. I'd like you to do just two things. You had said you were going to prepare a slide for us, and then based on the comments from the public audience, the comments really were not about the statistics or anything like that, with the one exception of the speaker, but really the public comments really focused on increasing the availability of lung transplants. So, in

your summary statement before we go to the break and deliberations, even if your device showed the same outcomes as cold storage, addressing the public comments, would you just summarize, after you show your slide, with how your device, even if it's not better, even if it's slightly worse, saves lives by increasing transplant availability? Because that's the message from the public that they want us to address.

DR. HASSANEIN: Sure.

DR. SCHWAITZBERG: So you've got 4 minutes.

DR. HASSANEIN: Thank you. First, the slide. I'd like to ask Dr. Gabriel Loor to present the slide.

DR. LOOR: Just to Dr. Connor's point. He asked for a very good analysis. So the difference between PGD3 at Time 0 that resolved, which would be considered transient PGD, is shown there. You buy an 80% 24-month in this cohort. If you had PGD3 at 72 hours and it remained, you went down to 52.5. However, if you had PGD 0 all the way along, that was the best survival at 87%. And of the patients that were here, one of them was mine and had PGD 0. The other one was from UCLA and was also PGD 0 within the first 72 hours.

DR. SCHWAITZBERG: Terrific. If you could now conclude before we go to the break.

DR. HASSANEIN: Thank you.

DR. SCHWAITZBERG: Addressing the public comment.

DR. HASSANEIN: Thank you. Thank you, Mr. Chairman, for allowing me the opportunity to address the public comments. I'll be very brief.

Looking at the INSPIRE trial results that we're sitting here looking at today, there's one mechanism that, based on the results of the INSPIRE trial, we can foresee a benefit to improve -- increase the availability of lungs from the INSPIRE trial results, which is the ability to reduce ischemic injury despite the longer cross-clamp time, which basically focused on longer-distance retrieval. As you've heard from some of the public commentary,

there were patients that are normal lungs -- we're not talking about extended criteria lungs -- just because of the distance, that we cannot utilize them. From the INSPIRE trial results, I think we can see that.

The second piece, which is not the focus of this particular Panel and not this trial, we have a large-sized trial called EXPAND Lung, focused exclusively on older donors, donors after circulatory death, and donors with low lung oxygenation, and that trial is ongoing, and we have the highest utilization out of that trial than any other technologies. But that is not the topic here. We are here talking about INSPIRE, and from INSPIRE, the lung cross-clamp time and the reduction of ischemic time provide us the ability to get lungs that are currently not being even considered just because of distance. Normal lung function, just distance is the issue.

DR. SCHWAITZBERG: Thank you. I'd like to thank both the Sponsor and the FDA for their presentations.

It is 2:48. We will take a 12-minute break. Panel members, please do not discuss the topics. We will reconvene at exactly 3:00.

(Off the record at 2:48 p.m.)

(On the record at 3:01 p.m.)

DR. SCHWAITZBERG: All right, we are back in session. We will focus our discussion on the FDA questions. Panel members, you have copies of the questions and the commentary. We will go around the room. If you have nothing new to add and you agree with some particular salient comment, you can say nothing new to add or I agree with somebody's comment. You don't have to extrapolate any further. We have 10 questions, we've got 2½ hours, it's about 15 minutes a question, so if the theme of this Panel meeting is that the Chair is whipping people to stay on time, then I'm doing it so that you can all get home.

So we will start with Question No. 1, and I'll read the first comment: The modified primary effectiveness endpoint represented by TransMedics was survival at 30 days post-transplantation and the absence of PGD (primary graft dysfunction) Level 3 within 72 hours post-transplantation, using per protocol population. This was modified from the initially approved primary effectiveness endpoint, which was survival at 30 days post-transplantation and absence of PGD3 at 72 hours post-transplantation, using modified intent to treat (mITT) population. Both endpoints were analyzed based on a non-inferiority comparison of success proportions in the two treatment groups, with the non-inferiority margin of 0.04.

FDA advised TransMedics against changing the primary effectiveness endpoint because 71% of the originally planned 320 subjects had already been transplanted and TransMedics may have been influenced by their monitoring of data. In addition, FDA has consistently recommended the mITT as the main analysis population due to potential bias associated with per protocol population. Furthermore, PGD grading at T0 may be susceptible to confounding, e.g., volume status if cardiopulmonary bypass was used or post-cross-clamp ventricular dysfunction.

This question has two parts.

Part a: Please discuss whether these results support a reasonable assurance of the safety and effectiveness of the OCS Lung System.

Table's in your packet for review.

And Part b, which we will ask you to consider at the same time: The observed difference in rates of PGD3 grading within 72 hours was driven by the T0 grading. Please discuss the impact of T0 episodes on the interpretation of study results.

After we've gone around the room, I will summarize the Panel's comments for Dr. Fisher and we will move on to the next question.

So, Dr. Yusen, I will ask you to start off, and we will head down the table and come around the room.

DR. YUSEN: You are going to regret that. Okay, I am going to --

DR. SCHWAITZBERG: I'm a glutton for punishment.

DR. YUSEN: Yes, this is Roger Yusen. I'm going to read some comments, which is going to take care of most of my -- many of my comments for the rest of this discussion.

DR. SCHWAITZBERG: I'm hoping you're going to take care of everybody's comments.

DR. YUSEN: No, so bear with me for about 90 seconds. So I agree with many of the comments, you know, that have been stated. Many of the concerns, especially from patients about too many patients dying with severe lung diseases, transplant potentially saving lives, improving quality of life, concerns about death on the lung transplant waiting list, allowing more time to find recipients to get a transplant done, concerns about geographic allocation of donor lungs, expand the donor pool, saving marginal lungs, etc. I also understand the desperate need to improve treatment of severe lung diseases and to improve the outcomes of transplant recipients. I also agree that the proposed technology has great potential to allow more transplants to be done, to diagnose and treat donor lung conditions, to prophylax against diseases and to improve transplant outcomes. However, most of these issues were not adequately demonstrated by the trial or formally addressed by the trial.

I have concerns about ticking off many of my colleagues and not supporting what I think is potentially great technology, but I think many biases challenge the validity of the trial, the ability to reliably interpret the results of the trial. Specifically related to the modified intention to treat did exclude many randomized patients. I have concerns about post-randomization screen failures, unbalanced protocol violations, limited information on randomized but crossover patients, the open label can affect post-operative management

and outcomes, the unplanned interim analysis, changes in the study protocol, etc.

Regarding the results, and I'm finishing up soon, this is a non-inferiority trial with lack of establishing non-inferiority in the modified intention to treat and the per-protocol for the endpoint that included the composite 72 hours, and a lack of establishing non-inferiority for the modified intention to treat for the endpoint that did include composite within 72 hours.

The PGD grading, from what I understand, the PGD grading was not confirmed; it was read from the case report form, and there wasn't a formal central reading, and so one of the key primary outcomes, I'm not sure about the validity of the grading. We saw worse short-term survival and no difference in long-term survival with the new therapy. We did see a lower PGD3 score within 72 hours, and you know, yes, there are potential benefits for increased preservation time which demonstrated a decreased ischemic time, but there are the many issues I've outlined.

So I would conclude by saying that with many of the study methodology biases that lead to -- they lead to questioning the validity of the study and the lack of superiority, a lack of non-inferiority, worse short-term outcome, no difference in long-term survival, etc., leads me to question this. And so to specifically answer this question, is there a reasonable assurance of the safety and effectiveness, I think, based on my longwinded answer, that I am not reasonably assured at this time.

DR. SCHWAITZBERG: Thank you.

Dr. Nathan.

DR. NATHAN: That's a tough one to follow, but I'll try and address the question on hand, and then towards the end I'll have further comments. I think that, in my mind, there is reasonable assurance of the safety even though it didn't -- if you look at the mITT, it didn't meet the endpoint of non-inferiority, and we can look at the 30-day survival, and I'm

also concerned about the drop-off and increased mortality, if you just look at mortality at 30 days. However, I will caveat that by saying that there haven't been many studies like this in lung transplant. We haven't got a good foundation for what the appropriate endpoint should be.

I think the post hoc analysis that the company did was an appropriate one in terms of looking at mortality in the hospital. There are many patients who make it through 30 days, and we barely get them to squeak by, and they die on Day 31, 32, or 2 months later in the hospital, and that's not captured as mortality, so I think there's validity to that.

And then also, if you look at the 1-, 2-year survival, there's no difference in outcomes between the two groups in terms of 1-year survival, 2-year survival. So, in my mind, I think it is safe, and I think, you know, what I was getting at, and this might come out more, is that if it allows more patients to be transplanted, then even though the survival at 2 years, there might not be a difference, but there will be more patients numerically who's surviving to 2 years.

DR. SCHWAITZBERG: Thank you.

Dr. Meyer. Dr. Meyer and then Dr. Moon.

DR. MEYER: Dan Meyer.

Regarding the first question in terms of safety, I think we talked about this a little, and I did have some concern about safety just from an early 30-day mortality risk and the issues that could be much technical in nature, but the company has discussed their strategy for potential implementation and experienced centers. And I would think it important to stress this, if there was an IFU for this device that would really limit the use by very, very experienced centers, because I think both the technical aspects that happened early as well as the vascular and cardiac aspects are really all likely related to the device and implementation of the device.

Second question related to the PGD3 and the T0 grading, that is also a concern, as we've heard, and analyzing this in another way perhaps with and without inclusion of the T0 but including T1 in 24, 48, 72 hours could be considered because it is heavily weighted for the T0, and I would be concerned about that.

DR. SCHWAITZBERG: Dr. Moon.

DR. MOON: I appreciate all the recipients that came and spoke today; they're very moving stories. It wasn't necessarily the OCS, though, that made that transplant successful. I think the data shows the SOC would've been probably equally good. Many of the public speakers spoke about what Dr. Yusen referred to, was increasing the donor pool, increasing the -- prolonging the time. This study didn't address any of that, so I mean, that's all probably going to be addressed in the EXTEND trial.

But in this trial, we're essentially trying to say this is better than or equal to the standard of care in a regular patient who's getting a regular transplant. And I think, sort of, I still have a bit of a problem with some of these patient -- I don't have a problem with screening failures; that's a patient's identified with pneumonia or something pre-, putting on the device pre-choosing what to do. But when you go back 2 years and change somebody out of the study because they didn't have an appropriate ABG and you know they didn't do well, I've got a problem with that.

DR. SCHWAITZBERG: Thank you.

Ms. Barnes.

MS. BARNES: You know, first, I appreciate the patients and others who are speaking on behalf of the patients, and you know, I think there does seem to be a reasonable assurance of safety. I, you know, do have some current concerns about the increased risk of respiratory failure. I keep in mind that most -- for most of these patients, death is not just likely, it's imminent for a lot of them, so I just want to keep that in mind as well. But I

can see that this technology, you know, if you look at technology in our history and where different types of technology have come from, I could see that in the future this might be a very important part.

MR. FRANKEL: Rather than echoing what has already been said, I'm going to just reserve some time for afterwards. I'll speak further then because I do agree with the sentiments that were made specifically in the beginning in terms of the serious concerns and, on the other hand, not wanting to stifle some extraordinarily important innovation. But because of the limitations that have been voiced throughout the day today, there's obviously substantial concern.

The question is, moving forward, whether using it in a more limited, more narrow way for those of unmet need, that's a question that I think that is still unclear, whether we do have a patient population that would be isolated where the standard of care would not be an option and that this would be able to be utilized specifically for that patient population.

DR. SCHWAITZBERG: Thank you.

Dr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla.

So I'd like to remind the Panel once again that this INSPIRE trial was first of its kind, so despite the challenges that it had in the study design, etc., the INSPIRE trial did meet the primary endpoint of survival at 30 days and the absence of PGD3 within the first 72 hours in the per-protocol population. The long-term mortality at 6 months, 12 months, and 24 months was equal between the arms, so therefore, we could at least say that there is a clear signal that the part is safe and to some extent effective.

The trial also showed that the OCS lung had better or equal in performance on the patient PGD3 at any time point in the 72 hours. Several studies have also shown that PGD3

at any time point, 0, 24, 48, or 72, is important for clinical outcomes. So those are my comments.

DR. SCHWAITZBERG: Thank you.

Dr. Connor.

DR. CONNOR: So, first, I would say I agree almost verbatim with Dr. Yusen and would go on to further add, you know, the fact that we're debating individual patients and whether they were on per protocol or not is really evidence why we should do ITT trials, that medicine is messy, transplant medicine is messier, and intent is the key, not whether patients followed protocols exactly, because that's very hard.

Second, looking at like ITT and per protocol in the SOC, the difference is four patients; three out of those four were successes. That's 75% and totally in line with the 71% overall rate. But in the OCS, we saw 11 patients be excluded; all 11 were failures. If the true success rate is 75%, the chance of zero out of 11 of those being successes is about 1 in 2 million. So the fact that there were such huge discrepancies when going from one of those populations to another is, you know, somewhere between dubious and suspicious maybe. Looking at the original analysis, the mITT on the original endpoint, it's actually statistically significantly better in the standard of care, 94.5% versus 87.9, with a Fisher's exact test is better for the standard of care, not -- not only is it not non-inferior, it is better.

That said, I agree that the 30-day endpoint plus in-hospitalization is actually more fair and should be considered. And that doesn't even get into this idea of screen failures, like when someone couldn't find an "on" switch, that that didn't count; that patient didn't count in the analysis when a battery died in a helicopter -- that patient didn't count in the analysis? I mean, all these things seem to make OCS less positive, again.

So I totally understand the point of view of patients, and that if this technology works, it can extend times and maybe for those, you know, hard-to-get-to patients or lungs

that we'd love to get out of Hawaii, it offers benefit, but there's very little evidence of efficacy within this treatment window, that this is better than what we're doing today, to me.

DR. SCHWAITZBERG: Thank you.

Dr. O'Connor.

DR. O'CONNOR: So this device has the potential to dramatically facilitate an increase in the number of transplants. But to answer the question very directly, you know, the outcome data largely fails to support non-inferiority and, you know, the intention to treat versus the per-protocol debate, in fact, harkens to an issue, and that is that in many clinical trials there's what we call fragility; that is to say, a small number of patients can shape a statistically significant outcome or not. And so this is a study that has a lot of fragility to it.

The longer-term outcome equipoise here that other people have already alluded to tells me that, you know, if you are willing to accept a slightly worse outcome, you could perhaps get more people to pretty good outcomes at a year or 2 years with this device. That is to say, even if you say the device is slightly inferior, it might be still worthwhile in the sense that it would allow us to do more transplants, it would allow us to take more time to evaluate transplants. But the direct answer to the question, were the non-inferiority criteria met, the answer is largely no.

DR. SCHWAITZBERG: Thank you.

Mr. Stammers.

MR. STAMMERS: Thank you. Al Stammers.

Reflecting on what this organization, this Sponsor, TransMedics, has done over the last 6 or 7 years and going back to the late 1990s is truly remarkable. I mean, this study involving the leaders in the world in regards to lung transplantation, impeccable credentials, brilliant minds who have been involved in all aspects of the study, is very

refreshing, and I think we all appreciate the tremendous amount of work that has gone into this endeavor, both on TransMedics' and the FDA's part.

I'm a perfusionist, and a perfusionist uses devices day in and day out, and the question with regards to safety I'd like to address from the technical standpoint. First of all, it really is an unfair comparison because you take this extremely sophisticated machine that has aspects to it that are used in cardiopulmonary bypass are beyond what we have, what we use every day for open heart surgery, some aspects, at least, and then you compare it to infusing a solution with ice, and you know, it really is very unfair.

And it's a little bit disheartening, from my perspective, because seeing this really, really advanced technology, almost an apples-and-orange comparison other than it's the standard of care since the advent of lung transplantation, I was hoping to see more robust outcomes that were more meaningful than dealing with, you know, very low margins of success in regards to the statistical significance.

So, to conclude, from a safety perspective, you know, I think the SAEs that we have seen are just related to the -- basically placing indwelling catheters and probably to be expected by any surgeon, and I think are minimal in regards to, you know, the potential benefits that eventually this technology may show.

DR. KRUPNICK: Yeah. I mean, listening to the discussions, I agree with a lot of points, but I have a feeling we're sort of missing the point and holding this to a much higher standard than is our intent. The simple question was, is this as effective as the standard of care, with the standard of care being fairly arcane. Based on how you do the analysis of data, I think the answer is yes.

Some of the salient points whether to treat, to look at PGD within 72 hours or at 72 hours, my personal bias is that PGD at Time 0 makes a huge difference, a huge difference to unplanned cardiopulmonary bypass and the long-term outcome. So I think that's actually

the right point to look at it.

Some of the failures that were brought up, I mean, a lot of that is operator, surgeon, whatever you will call a decision that the company can't control it, quite frankly. We can't speak to the person who's looking at the organ and making the decision in the field, and I doubt very much the company was involved in minute-to-minute decisions, so these were decisions by a surgeon, so we can't really penalize for it.

The data seems that they've met -- it seems that the device has met the criteria that it was supposed to meet, that it's -- there is a similar outcome to standard preservation, and some of the salient points, I think, we're over-reading, over-reaching and holding it to a little bit of a higher standard than what we're asked to do. So I think, you know, they've fulfilled their kind of requirement to prove the non-inferiority.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: Thank you. It's Victor van Berkel.

So I would like to say that I agree with both Dr. Yusen and Dr. Moon on the majority of their comments and I suppose say that we are all very excited about what the results of the EXTEND trial are going to be, since that is where the majority of the public comments were centered upon.

To directly answer the questions for (a) and (b), I would say that I think that there is a reasonable assurance of safety but not a reasonable assurance of effectiveness. And to disagree with Dr. Krupnick about part (b), I do not think that T0 PGD3 has much impact on long-term patient outcomes. I know the three papers that have been presented, I have looked at that data very carefully, and I think that the reason that the 2016 recommendations are changing is because there's a lot of variability in how people score PGD3 at Time 0, and it's not very reliable. And I think, in the face of that data, that makes me worry about using that data more centrally to this particular application.

DR. SCHWAITZBERG: Thank you.

Dr. Hammon.

DR. HAMMON: I agree with Dr. Krupnick.

DR. SCHWAITZBERG: Thank you.

Dr. Afifi.

DR. AFIFI: I wish we had the data to do a true intent-to-treat analysis because that is the correct way to analyze the data according to clinical trials methodology. We don't have that. So the best we could do is look at the modified intent-to-treat, and based on that, I do not have reasonable assurance of safety. I do have reasonable assurance of effectiveness.

DR. YUH: Thank you. Yes, I don't have much to add to the conversation, but in terms of safety, I think looking at the totality of the data, I don't think this is an unsafe device, especially under the conditions that it's being used to operate and the patient population it's being used to address. So although it's failed in several testing scenarios in that regard, in looking at the data and looking at the failures, I don't think it's an unsafe device. In terms of its efficacy, that's more doubtful to me for the reasons that I explained earlier; it's just that the change in the definition of the primary efficacy endpoint midstream when the majority of the enrollment was completed just bothers me. It may not prove out in terms of looking at the interim -- looking at the interval analysis, but it still bothers me, and I have to look at the data, and it's an important portion of this study.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: Jeff Riley.

My perspective is similar to Al's. I'm a perfusionist; I educate perfusionists. I'm on a lung transplant team, and I've been on two lung transplant teams in the past. We have a lung transplant patient on ECMO, and we're doing a lung transplant right now back home. And the words that I heard, the word "messy," these types of studies are messy, and when

you get the talented pool, the talent pool together to do the study that Al referred to, I'm impressed with the organization and the integrity of TransMedics.

I've worked with a lot of device manufacturers for 40 years. The first organ preservation machine I got to run was a Belzer kidney preservation device, and we thought that was going to be the future, and now here it is, 40 years later, and we're finally in the future.

I'm convinced that it's safe, and I think the positives outweigh the negatives, and I'm okay with its effectiveness.

DR. SCHWAITZBERG: So, Dr. Fisher, if I can summarize. The opinions are split. There are significant concerns by some of the panelists concerning the validity of the trial conduct, particularly with the change in endpoint in spite of the FDA's request not to change it this far into the study. For some panelists, this meant that they do not believe that the company had demonstrated the requisite either safety or effectiveness, but even with that, it's split where the majority of the Panel felt that it was reasonably safe but maybe not particularly effective. Other members of the Panel looked less at the fine statistical analysis, looking at the big, big picture, trying to ignore what is not a study question about increased organ availability because that's really not what's in question here.

And so the bottom line for the Panel is there are serious concerns about the validity of the trial, post hoc protocol violation scoring, and the decision to use the per-protocol. However, there was additional support for the fact that they looked at the per-protocol population and felt that that was acceptable. And it will ultimately come down to what the final vote is. Does that answer your question?

DR. FISHER: Yes, I think so. Thank you.

DR. SCHWAITZBERG: Terrific. Item 2: Despite 1:1 randomization, there were disproportionately more screen failures and major protocol violations among OCS-

randomized subjects compared to standard of care-randomized subjects. Sixty-four percent of "screen failures" were transplanted "off-study." The disproportionate removal of subjects jeopardized the property of the randomization and may have introduced selection bias into the safety and effectiveness analyses.

You have a table in front of you.

There are three parts to this. I will ask you to comment on all three.

Please comment on the impact of post-randomization screen failures and protocol violations on trial interpretability, and the relative significance of mITT and PP analysis.

Basically, what it's asking you is to decide whether you think that this is an important -- features of how you will make your decision, and try to stay focused on the actual question.

Item (b): Given the number of donor screen failures, is additional clarity needed to define which lungs should be accepted for treatment with the OCS system?

Item (c): The 7 user errors identified in the table above were all primary effectiveness endpoint failures and included 2 deaths by 30 day post-transplant. Furthermore, while turn-down of conventionally preserved donor lungs is usually a rare event, at least one turn-down appears to have been the direct result of device malfunction.

Please comment on the benefit-risk of the OCS system in the context of the device complexity and reliability, and the impact on donor lung utilization.

And we will start on this side of the room with Ms. Barnes.

MS. BARNES: So regarding the complexity of the devices, and I think, obviously, they're complex even though I can appreciate that many of the users are describing a good user interface and an easier way of using the device. But, you know, this type of technology is obviously going to take training; they have a training program. I think that where there are opportunities for failures, there will be. And so you have to cover for that, and I think,

you know, maybe the benefit is, one, you have the access to the technology. The risk is you use the technology and it fails. So maybe having backup programs, backup systems that are available could help change that complexity.

And I think that, you know, as far as the technology goes, I think that there isn't really -- there aren't lots of choices for these surgeons right now, and so therefore, there aren't many patients' choices either.

So I think, you know, from a benefit-risk perspective, I'm not thrilled with the failures; I'm not thrilled with hearing that there were, you know, some deaths as a result of those failures. But I also understand that it's also a learning process with the technology and with the scientists.

DR. SCHWAITZBERG: Thank you.

MR. FRANKEL: So, in terms of (a), I think that that would not be the focal issue, in my mind, the way that I'm perceiving it, but it is essential in the totality of looking at in the context of everything else that was discussed today.

For (b), FDA had noted a lack of clarity in some of the criteria and exclusion criteria, inclusion and exclusion criteria. So I think that it would be helpful, definitely, moving forward, that that is no longer an issue, that there should be additional clarity where there's nothing ambiguous in terms of what specifically this will be used for in terms of lungs.

For (c), the issue -- I think that it's really a fundamental issue where, for consumers, looking from that perspective, that I typically want to empower the consumer with making decisions for themselves between one technology and another and one therapeutic and another, and I think that by the nature of lung transplants, and I would definitely appreciate if any one of the experts here can say otherwise, there will not be much in terms of options, say tomorrow that this is implemented in a center that will be utilized, there won't be a choice left to the patient.

So I think that it's very important to look at the deaths involved and failures potentially due to the device itself, that if a patient is going to choose that, that they're aware of those risks that may be introduced that aren't in the standard of care. And if they don't have that option, that's concerning to me that it's going to be used for patients that may be able to fare better with the standard of care. Obviously, if it's used narrowly for those that would not be able to be treated by standard of care, whether it's for geographic distances and whatnot, then I would obviously support that because there is no -- there's an unmet need without any alternative option.

DR. SCHWAITZBERG: Thank you.

MR. THURAMALLA: Naveen Thuramalla.

So we all agree that there is an imbalance in the screen failures between the two arms, but as explained by Dr. Ardehali and other clinicians, when we look at the characteristics of the donor lungs that were actually transplanted in the study, there was no evidence that this imbalance resulted in any significant difference between one arm versus the other. Also to note that the lungs transplanted in the OCS arm seemed to be less healthy than the lungs transplanted in the control arm. Despite this, the 30-day plus the in-hospital mortality was equal between the arms. Thank you.

DR. SCHWAITZBERG: Thank you.

Dr. Connor.

DR. CONNOR: Jason Connor.

So, I mean, I think I would -- may respectfully disagree with the last point because we actually don't know all of the outcomes for all of the screen failures, so it doesn't seem like there are differences in terms of baseline characteristics, but I don't know that we can definitively say there are not differences in outcomes.

I think I largely covered (a) and (b) actually in my last one, that they're concerning.

But in (c), just from good clinical trial practice, 7% of the time user errors occurred, and all seven times those were failures, and they didn't count in the primary analysis. I can't like that -- I've just never seen a clinical trial where a user error using a product which results in a failure, not that it directly results, but excluding that from the primary analysis seems like an extremely rare thing and not good clinical trial practice to me.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: So this is a discussion of how hard it is to do clinical trials. You know, donor screening failures are a part and parcel of lung and liver and heart transplantation, and I'm not surprised that they're not equal across the two groups, and so I don't get too excited about that.

With respect to a need for additional clarity, I think that with time and experience with using this technology, if it gets approved, they'll learn better how to evaluate people with it. And so it's not so much the status of the data that we're given, but rather what we anticipate the future would be if the device gets the go-ahead, and I think that they'll be fine. The seven user errors identified in the table above, once again, I share Dr. Connor's concerns about that.

DR. SCHWAITZBERG: Thank you.

Mr. Stammers.

MR. STAMMERS: Thank you. Al Stammers.

I'd like to follow up with what both Dr. Connor and Dr. O'Connor had both commented on but from a little bit different angle. The user errors, I think, draw attention to not only safety but also to some of the screen failures that occurred, and if you look at most of the logistic screen failures in the OCS treatment arm, they were -- many of them were device related. And I know Dr. Hassanein tried to tell us how easy this device is to use, and several of the public commentators stated that it seemed to be very

straightforward. I think, looking at the data there, that would be somewhat contradictory to what we have seen, and the fact that the application on the iPad, the tablet, is making it easier for the end users to answer the wrong questions, that may be good or may be worrisome, and I don't know quite how to interpret that other than it was probably a pretty subjective comment at the time.

There are some issues that we're not addressing necessarily with these three questions but I think are part of the screen failures, and I think it was brought up, perhaps, by some of the surgeons. And, you know, you have this device, which is normothermic, and the rapidity of which type, any type of ischemic injury is going to occur, once they fail on the device, you know, it raises concern. And I'm sure that the backup protocols, you know, once this device was to fail, was to revert to SOC and administer cold solution quickly to preserve the organ. But I think the point I'm trying to make is I think with these screen failures, perhaps with time, better knowledge, the training that was mentioned earlier in regards to a team comes out to Andover and receives this training, goes back and then, oh, unfortunately, one of the team members might've been off call when a lung came in and they couldn't use the device, you know, that clearly is going to be corrected. You can't have such a small number of individuals who are trained in this technology, and I think if you do expand it, you'll see some of these screen failures, and the way I look at it, about a third of them in the treatment arm of OCS may go away with better technological education.

DR. SCHWAITZBERG: Thank you.

Dr. Krupnick.

DR. KRUPNICK: Yeah, again, I'll just echo my last point that we're holding a very complex device with multiple teams involved to the same standard as if this was a simple trial that was randomized where there was a sugar pill versus a blood pressure pill given. Those are simple trials to do and some of the echo -- sentiments I hear echoed treat this as

one of those type of randomized trials. It's impossible to blind somebody -- it's impossible to take a surgeon or donor, the harvesting surgeons out of the loop, so some of the screen failures were explained by the harvesting surgeon.

Machines fail all the time, Dr. Connor. I mean, think about this discussion if we were right now looking at ECMO, which fails all the time and has all sorts of problems. It would actually -- the fact that only one lung has had a machine failure, I think that's great. If you look at the number of problems with bypass circuits, with ECMO circuits, it happens every day. I think the fact that a brand new device had one failure is great. Again, we have to hold it to a realistic standard of care, not a simple one as you would for a placebo drug trial.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: Thank you, it's Victor van Berkel again.

So I don't have anything new to say about (a). About (b), I would say that talking about additional clarity, you need to define what lung should be accepted, and I would say absolutely, I think that that was demonstrated by the fact that there was an argument about what qualified as pneumonia, and I think that on the inclusion and exclusion criteria, that there -- we just had an active pulmonary disease or confirmed pneumonia when all the pulmonologists in the world can't actually decide what qualifies as pneumonia. Is it x-ray, is it white count, is it, you know, something on the bronch? I think having some more specific details that would allow someone to more definitively say this person, you know, should or should not be included or excluded from the study would've alleviated some of these difficulties.

And then, finally, to again -- apparently me and Sasha are going to play point and counterpoint here -- one of the things that worries me the most about this is that one failure because that is a set of lungs that was wasted. We can't afford to waste lungs. If those lungs had just gone in the cooler, they would've gotten transplanted into somebody,

and because we did this thing that is more complicated -- and I'm not diminishing the role of this. I mean, it's an incredible device, but it is -- as has been said before, it's apples and oranges. This is a very complicated thing, and if there is an error that happens and we lose lungs because of that that we have not lost, that is a shame.

Perhaps that is a risk worth taking if we can demonstrate that there is going to be benefit, but I would say that the data that we have here does not demonstrate a marked benefit. I don't think that you can really say that. We can argue about, you know, non-inferiority, but there's clearly not a huge step forward. And so if there's a chance that we are going to lose lungs by putting them on the machine, then even though there's only one lost, and I appreciate that and I know that that is an incredibly high bar to try to clear, that's still one lung that was lost.

DR. SCHWAITZBERG: Dr. Hammon.

DR. HAMMON: Well, I'll take a lot of these comments, including my mate over here, Dr. van Berkel, with all of the good intentions that they manifest, however, there's an old saying in the -- down in the Ozarks, where I grew up, that the road to hell is paved with good intentions, and what we need to do here is improve health care. And I know Dr. Wallwork, who's probably the one person in the room who has more experience just from a year-year-year standpoint, as I do, remembers the very early years of lung transplantation when it was like an absolute morbid stew of people running around, trying to do things to help the patients when we didn't have enough help and we didn't have enough blood and we didn't have enough medicine, and it was a tough time. And things have improved so much, it's just incredible.

So I guess what I'd say to all three questions would be, yes, something went wrong, something didn't go right, somebody who was trying to do the best thing didn't do the best thing, but that was a relatively small number of mistakes. Now, this is clinical research, and

this is an ethical issue, and I have a feeling that the company persons who spoke to us today and some of their assistants probably anticipate the idea that with their data being torn to shreds by what a lot of people said today, that they will take a much better attitude toward the ethics of clinical research.

DR. SCHWAITZBERG: Thank you.

Dr. Afifi.

DR. AFIFI: I already expressed my feeling and my belief about intent to treat versus per protocol, so I won't belabor that. But I wish there was more clarity, at least from my point of view, about the imbalance in terms of screen failures and protocol violations between the two arms. We know that there is an imbalance, but it's not clear to me what the reasons for those are.

DR. SCHWAITZBERG: And device failures?

DR. AFIFI: Pardon me?

DR. SCHWAITZBERG: And part (c), the device failures? And the errors --

DR. AFIFI: Yes, that too. That as well.

DR. SCHWAITZBERG: Okay, great.

Dr. Yuh.

DR. YUH: So, in spite of the imbalance of the screening failures, I was reasonably reassured by the Sponsors pointing out that the quality of the lungs were not, at least by the criteria that they were using, negatively impacted. So the screening failures in and of themselves don't bother me as much.

In terms of the additional clarity for donor screen failures, I agree with Dr. Connor; it's really going to come with experience with the device and to determine what current criteria that we use for the quality of lungs and then future criteria that might be tailored to the use of such a system might be applicable, so I think that will just come with experience

in using the device.

In terms of the user errors, I think that can be addressed with better training down the road with a very complex device that, you know, when you think about what it's being asked to do, I think it's pretty remarkable in terms of its design. And so I think those types of -- with any new device, you're going to have user errors. Your engineering challenge is to create a device that minimizes the chance of that, and I think that that's certainly within the realm of possibility here.

DR. SCHWAITZBERG: Do you lump the protocol violation changes with the screen failures, or do you consider them -- the impact on the trial differently?

DR. YUH: I pretty much lump them together, yeah.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: Jeff Riley.

Definitely the protocol is flawed, but I thought you did a great job of drawing the question out for (a) on the different populations. I think it did affect the results.

For number 2, given the number of screen failures, I don't think -- I actually think all lungs can go on this machine. I think one of the hopes of the future is that you could put a lung with pneumonia on this machine and perhaps bring it back to -- make it transplantable. And maybe the device needs a hand crank for the helicopter power failure.

(Laughter.)

DR. SCHWAITZBERG: Like the good old days.

Dr. Yusen.

DR. YUSEN: Roger Yusen.

Just a couple comments to add to what I said before, comments of the others. The discussion I'm hearing relates to what people wish they had, and I'm thinking more about what I think this study showed and what it didn't show. And so yes, I'd like to have a better

technology; yes, I'd like to have, you know, a technology that does what we hope it does, but I think we need to look at the data and the quality of the data and the quality of the study.

You know, we look at the baseline characteristics of the patients, and they're similar, and we're talking about the safety's not so different, the outcomes, you know, aren't so different, and this can help in other ways, potentially. But, you know, the beauty of randomization is the known confounders and the unknown confounders get randomized out. But here, you know, patients were sort of plucked out after randomization, so I won't get too repetitive there. But, again, the baseline characteristics are of a smaller cohort than the entire cohort, so I don't know if they're different.

And then you think about in terms of safety and risk-benefit, you know, there might be rare or less common outcomes that we don't know about, and yes, patients might have been steered into one treatment arm versus another, and you might say "but the baseline characteristics are the same." Well, in a subgroup they are close, maybe those aren't all the important characteristics. So I still think, you know, there are many methodologic concerns here that affect our interpretation of the risk-benefit.

And then, finally, regarding the clarity needed for the study, I think it's typically useful to clarify eligibility criteria for a study. But, again, you know, if patients are -- maybe that's not so important if they're randomized and that is equally distributed into both treatment arms.

DR. SCHWAITZBERG: Thank you.

Dr. Nathan.

DR. NATHAN: Yeah, thanks. Steve Nathan.

I agree with my two colleagues, Dr. Krupnick and Dr. Yuh, that these studies in lung transplant recipients are very, very difficult to implement and do -- and, in fact, when I last

checked, I think we just had one FDA-approved product for lung transplantation, and that was Perfadex. Thankfully, we can borrow from our cardiac and liver colleagues and our renal colleagues to use drugs that actually prolong patients' lives.

So having been involved in a number of lung transplant studies, there certainly are different confounding factors that make it very difficult. I think these protocol violations and screen failures we don't want to see in a clinical study, but you have to put it in a context of a very difficult patient population, many moving parts happening at the time of transplantation, surgeons going out, trying to orchestrate all of this. So I'm not too concerned about that; that's just the reality of doing a lung transplant clinical trial.

I think one point I would like to make is the difference between undertaking a clinical trial and what happens in clinical practice. I think, inherently, when folks are involved in clinical trials, the goal is to get patients randomized into a clinical trial and to populate the clinical trial, and so there's added pressure to go out and put patients on the device, and I think that's how it will be used in clinical practice if it becomes available. I think Naftali alluded to the fact that it might just be used selectively for tough cases where the surgeon needs more time to explant the lungs or enable the surgical team to go out and get lungs that are 2,000 miles away instead of 1,000 miles away. So I don't think all patients necessarily will go on the device, and there will be certainly patients who you can use standard procedures to do the lung transplants. I think the benefit-risk is there, especially because of what I just said in terms of the benefit and ability to go out and get more lungs.

DR. SCHWAITZBERG: Dr. Meyer.

DR. MEYER: Dan Meyer.

And I'll echo what Dr. Nathan and others have said, that -- and I'm kind of lumping 1 and 3 or (a) and (c) together. I was, you know, bothered to some extent about the screening failures and the protocol violations, but as we heard, the baseline characteristics

were similar between the two groups, and in a perfect world, some type of post hoc analysis with crossovers, as we've talked about before, could shed some light into the outcomes, but I don't know if that's a realistic request.

And then in terms of (b) and clarity, I just think that with education and, you know, really sticking to the guidelines for inclusion, I think that will improve over time.

DR. SCHWAITZBERG: Thank you.

Dr. Moon, who will go first next time.

DR. MOON: Great. The screen failure issue is fine by me. I think it's okay to determine at the time of harvesting whether you're going to use a device or not. I mean, that's part of the assessment. The patient who had the ABG June 2014 and then had a note added to the chart July 2015 that said the ABG wasn't in enough time was determined after we knew the results of that patient. And I'm not exactly sure how the functioning of that occurred, but for me to imagine that the center was looking at their data that closely and said, oops, we made a mistake a year ago, let's change it, is difficult to imagine.

I'm also not worried in the user error because I think that will improve, like Dr. Yuh said, with better education, a better device, and more improved technical expertise. But, you know, once the patient is on the device and in the study, taking them out later is invalid, to me.

DR. SCHWAITZBERG: So I understand your answer, you appreciate the fact that user errors occur, but taking them out of the study is what you had an issue with?

DR. MOON: Well, I think they have to be considered, yes. Or at least the data presented for those as a separate group.

DR. SCHWAITZBERG: So to summarize Question No. -- go ahead.

DR. FISHER: Excuse me, thank you very much. If I could, before we summarize, you know, I've heard some of the panelists talk about what could happen in the future. I've

heard some of the panelists talk about, you know, these technically sophisticated machines and how they should be maybe held to a different bar. I've heard some other comments, but for me, life is complicated, all right? So what I need to do is, I need to take this study, right, and I need to look at the study, and I have to make a decision on it, and when I'm looking at it, I'm looking at the comparison of the device against an ice chest. I mean, that's it. So I have to take into consideration the failure rate of an ice chest. So I have to make that comparison, right?

But here's where I'm going with this. I didn't hear a whole lot of discussion. It talks about the benefit-risk of this device, but I only heard a couple panelists talk about what they really felt about these -- the technical sophistication of this device in this study and what its impact was on donor lung utilization. So I don't want to completely just dig into the weeds, but if we could just go around real quick and see if anybody has a comment on specifically that point, that would really help me out.

DR. SCHWAITZBERG: So if I can summarize just that point of the question to refocus the question for the Panel, everybody appreciates how incredibly sophisticated the device is and the effort and the years that have gone into this. Everybody appreciates that devices do fail. And I think what the issue to the question is, is that whether or not those devices that failed and were subsequently removed from the analysis impact, how we should interpret the safety and efficacy for the trial.

All we can really do is vote on how this trial came out, and what I'm asking you to consider, to try to refocus Dr. Fisher's question, if I might, and correct me if I'm in the wrong place, nobody's arguing that devices are complex, and they fail, they fail every day. The question really is they were removed from the trial. Does that affect the way we should interpret the closeness of the non-inferiority margins and how they hit their targets?

I'll start with Dr. Moon, and we'll go backwards, so you still get another shot. So if

we could stay focused to get to Dr. Fisher's question.

DR. MOON: I know you summarized the question, but it still is a bit sketchy, I think, but --

DR. SCHWAITZBERG: Should the patients who failed have been in the trial, and does it affect the way you think about it?

DR. MOON: Yes.

DR. SCHWAITZBERG: Dr. Meyer.

DR. MEYER: Yes.

DR. SCHWAITZBERG: Dr. Nathan.

DR. NATHAN: I think I interpret the question a little bit different in terms of you're asking about benefit-risk, and the patients who have protocol violations or who weren't included, I think, at the end of the day, a small number or less share the same kind of distaste for the integrity of the study because of it, but I think the risk and danger is we shouldn't throw the baby out with the bathwater by, you know, saying the risk and the data is no good because of those patients.

DR. SCHWAITZBERG: So your answer is no?

DR. NATHAN: Correct.

DR. YUSEN: My answer will be yes, but I need to make another comment. So I also heard a different question, and in terms of increasing the donor pool or not having to get rid of donor lungs, I don't think this study addressed that issue. And so I think we can hope and we assume that this technology will improve donor lung utilization, but this study didn't address that. And I'd like to put that into context in less than 1 minute in that the study was not able to hit a non-inferiority endpoint. It was not superior, it did not reach non-inferiority threshold, and it didn't address that issue.

DR. SCHWAITZBERG: So, Mr. Riley, the failures, should they be included in the

analysis, and would it affect the way you interpret this study, not the access to future lungs?

MR. RILEY: I'm going to say no.

DR. SCHWAITZBERG: Okay.

DR. YUH: So, you know, device failures are part of the whole picture, so yes, I think they should be included.

DR. SCHWAITZBERG: Would it affect the way you interpret the study?

DR. YUH: No.

DR. SCHWAITZBERG: Okay.

DR. YUH: It would not.

DR. AFIFI: I would say yes.

DR. SCHWAITZBERG: Okay.

DR. AFIFI: They should be included.

DR. HAMMON: If you had a book that had a picture of all these patients pre-op and post-op, you'd be amazed at how good they look, even the ones that had protocol violations. The one that died probably is a sore thumb, but a very small sore thumb. So my comment would be no.

DR. SCHWAITZBERG: Thank you.

Victor.

DR. VAN BERKEL: My comment would be yes.

DR. KRUPNICK: My comment is no, but I want to add we're ignoring certain aspects where even the standard of care leads to discarding the organ, including delayed planes, transportation difficulties, which happen quite frequently, especially in distal areas, so the answer is no.

MR. STAMMERS: No.

DR. O'CONNOR: Yes and no.

(Laughter.)

DR. SCHWAITZBERG: Thank you.

DR. CONNOR: Yeah, I mean absolutely. I think we're forgetting for the seven user errors, if the device fails -- it's a new device, it's ideally a great device, that's fine, but when the device fails, you can put the organ on ice. And it's a non-inferiority trial, which means if we had devices or lungs crossing over from the OCS group to the standard of care group, we're treating those patients the exact same way. Treating patients the exact same way in a non-inferiority trial helps the sponsor, right? And so there's no reason not to include them because they can still be treated and need to be, so all I'm saying is we have to count them.

MR. THURAMALLA: I would say no for the reasons for -- by Dr. Hammon.

DR. SCHWAITZBERG: Okay. Mr. Frankel.

MR. FRANKEL: I think that they should be included. I think that the difficulty with every clinical trial and comparing it to real world evidence is always pronounced, and in this case, I think that this is a substantial factor, and it is in the real world that these incidents will occur, and I think that they have to be evaluated accordingly.

MS. BARNES: Yes, I do think that the information on those patients should be included, not only for the evaluation of the product but also because it's clinical trial information that needs to be included longitudinally. Understanding how patients were affected long term or short term is important. And regardless of the outcome, sometimes you learn a lot from all types of studies, so I think that's a learning that we need. But I don't think it affects the way I see it.

DR. SCHWAITZBERG: Okay. So to try to summarize, the complexity of the device is appreciated, and devices will fail. For some of the panelists, the failures that do occur that

push this statistically further away from meeting the non-inferiority threshold are meaningful, and for others, they appreciate that those results should probably be included, but it wouldn't affect the way they would feel about their ultimate decision to approve or not approve the device.

Many people recognize that the protocol is flawed. There was some support for the fact that the Sponsor made some case for showing the equivalence in the per-protocol groups were equivalent, but it was pointed out that there are other factors than what goes on the list that may introduce bias, which is the basic reason for intention-to-treat protocols to begin with, with hundreds of patients to be included.

So, yes, there is concern that these cases were not included in the analysis, but it did not affect the way every Panel member felt about the potential safety and effectiveness of the device. Does that meet your questions?

DR. FISHER: I apologize for extending the time, but I really appreciate the extended discussion. Thank you.

DR. SCHWAITZBERG: All right. If this was easy, there would -- no. We're out of time. That's the part where you only get invited by the Chair.

Item 3: FDA believes the PGD grading scheme used by TransMedics does not represent pre-specified criteria (2005 ISHLT Consensus Statement); specifically:

- Assigning PGD3 in the setting of "prophylactic" ECMO may not adequately account for post-operative pulmonary dysfunction superimposed on the pre-operative ECMO indication. Note that prophylactic ECMO was used primarily at one site, and this site enrolled 24% of the patients.
- Parsing PGD grading on the basis of intubation status is not a part of the Consensus Statement grading scheme.

Please comment on the -- oh, only one question this time. Please comment on the

impact of the unplanned modification to the PGD grading scheme on the interpretability of the trial's effectiveness results.

Please confine your comments to how this impacts whether the trial results are interpretable.

DR. MOON: ECMO messes up every analysis of this, so it's very, very difficult. I'd have to sit with this and study it over and over again, and somebody should have.

DR. SCHWAITZBERG: Okay. Dr. Meyer.

DR. MEYER: Looking at the issue about the one program that uses ECMO prophylactically, the main one, looking at their data, it looked like both groups were equally affected, used ECMO in both groups. And so, for me, it really didn't negatively affect the interpretation.

DR. SCHWAITZBERG: Dr. Nathan.

DR. NATHAN: I think it does muddy the waters a little bit, but I think whichever way -- and certainly the ECMO patients do -- and I didn't get a good sense of how many there were, I think they were like 9% versus 16%, if I recall correctly. So I think whichever way you look at primary graft dysfunction, be it T0, T72, and how you define it, you could argue it both ways. These definitions that we come up with and change are kind of manmade definitions, and we like to stick to what the ISHLT tells us to do, but you know, there are many ways to look at primary graft dysfunction after transplant.

So it does muddy it, but it doesn't affect my interpretation of the data. I think that's why, when I look at the totality of the data, the thing that I mostly look at is outcomes and survival and more long-term outcomes, and certainly, I'm worried about what I see in the curves underneath with the OCS curve going down quite sharply, but it appears to equilibrate after about 6 months.

DR. SCHWAITZBERG: Dr. Yusen, interpretability with ECMO.

DR. YUSEN: I will stick with your question. So, in terms of interpretability, I do not think that the PGD grading scheme was completely consistent with the 2005 grading scheme, again, the study's PGD grading scheme. I do have concerns about the prophylactic ECMO use and especially with one center having very high enrollment and being the primary center driving that issue.

And then in terms of the unplanned modification to the grading scheme, yes, it completely changed the event rates of the trial. And, again, we've talked about PGD being an event, getting the same weight as death. And so I think, you know, all those issues raise some questions, and I wish the ECMO issue would have been addressed in a pre-specified subgroup analysis.

DR. SCHWAITZBERG: Any intubation issue?

DR. YUSEN: And yeah, I just -- I think all these could affect the outcomes, and it's just not the same grading scheme as the 2005 classification.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: The lack of the protocol being very specific on ECMO and the intubation is unfortunate, but I think it's explained. I think reviewers of the publications that will come out in the INSPIRE trial will take all these into consideration and mention them in the discussion and bring it out. So, to me, the last question is no.

DR. SCHWAITZBERG: Okay.

DR. YUH: So, first, the deviations from the ISHLT consensus did give me some positive -- and I looked at the data, it's 2005. And lung transplantation is a continually evolving field, and certainly with the rise of ECMO, the preponderance now -- double versus single lung transplantation changes in how we manage lung transplant recipients. Even selection criteria have changed. And so I think, given that the Sponsor, their explanations for these changes or deviations from the standard consensus are plausible, understanding

that it didn't really interfere with my interpretation of the data per se.

DR. SCHWAITZBERG: So you found it acceptable?

DR. YUH: Yes.

DR. SCHWAITZBERG: Okay. Dr. Afifi.

DR. AFIFI: This is largely a clinical question, so I'll let it -- I'll leave it to the clinicians on the Panel to comment.

DR. SCHWAITZBERG: Dr. Hammon.

DR. HAMMON: Well, I'll try and take that one. This conversation on this particular point reminds me of what we have every Thursday afternoon in the death and complications conference at our medical center, and what we are doing is we're debating whether or not these people made a mistake or whether they did the right thing or whether it was some place in the middle. But usually these things come out particularly when you've got cardiologists and surgeons or pulmonologists and pulmonary transplant surgeons talking to each other, is that some of these patients aren't going to do well, and in the present time we have a much better survival and a much better functionality system and a much better functionality in the recipients, and I believe that you can explain it however you want to, but this thing is kind of working out like it's supposed to.

DR. SCHWAITZBERG: Okay, Dr. van Berkel.

DR. VAN BERKEL: So I would say the reason that we have consensus statements is so that there is uniformity in how things are published and how people understand when you say that somebody has PGD3, what that means. I think that if we are not going to pay attention to those consensus statements, then the major thing that they are saying is that we have a benefit in PGD, but that PGD is different from what everyone else is thinking of when they think of PGD. I'm being extreme in saying that, and obviously, they haven't made a huge change, but why else would we have the consensus statement? And so, yes, I

think that the fact that they did not follow the consensus statement affects the interpretability of the results.

DR. SCHWAITZBERG: And are you also referring to the parsing on the basis of intubation?

DR. VAN BERKEL: I am.

DR. SCHWAITZBERG: Okay. Dr. Krupnick.

DR. KRUPNICK: Since the altered grading criteria, you can believe whatever you want to about consensus statements, but 10 years is a long time in the lung transplant field. It was not selectively applied to one group or the other, so you're still comparing apples to apples, so I don't think it affects the results at all.

MR. STAMMERS: Al Stammers. Did you -- okay, thank you.

The fact that ECMO was used prophylactically and resulted in a 96% success rate -- and Hannover also was mentioned. UCLA, I believe, used 14%, or 14% of the total patient population, I'm not quite clear from reading the documentation. I think this shows how useful this technology is and evolved over the last decade or so, and I don't have any problem with it being included, nor the intubation.

DR. SCHWAITZBERG: Thank you.

Dr. O'Connor.

DR. O'CONNOR: I share everybody's frustration in the impact of ECMO on our ability to evaluate PGD scoring. I'm not going to add anything to that. You know, for myself, since 2005, non-invasive ventilation has been used extensively in people with respiratory failure. And so saying that you've got somebody on high-flow nasal cannula or BiPAP who's in respiratory failure, and because they're not intubated their PGD score is 1, you know, it's not appropriate for either arm of the study, from my perspective. And so my biggest concern is their use of intubation as a way to kind of bifurcate how they evaluated people in

this study; it's my single biggest concern. And that's important because that, in turn, shapes their composite endpoint, either theirs or the FDA's, with PGD3.

DR. SCHWAITZBERG: Thank you.

Dr. Connor.

DR. CONNOR: I agree with Dr. Afifi, that I will leave this one to the clinicians.

MR. THURAMALLA: Naveen Thuramalla.

So from the clinicians' presentations we had today, I think my understanding is that the grading scheme applied was per the standard clinical practice that is followed in the lung transplantation. Again, the clinicians may disagree, but that's what I gathered from the presentations today. Also, like some of the panelists mentioned, the grading scheme was applied equally between both arms. So I think even if there is any impact, that would be minimal.

I'd like to also add that to avoid any confusion down the line with future post-approval studies, I think it would be beneficial for the Sponsor, along with their clinical collaborators and FDA, to discuss this thoroughly and agree upon the interpretation of the consensus statement so we won't get into this situation again. Thank you.

DR. SCHWAITZBERG: Mr. Frankel.

MR. FRANKEL: I agree with Dr. Nathan's remarks.

MS. BARNES: I largely defer to the scientists regarding their opinions, but I am inclined to agree with Dr. Nathan's evaluation.

DR. SCHWAITZBERG: All right, Dr. Fisher. Nearly all the panelists agree that the presence of ECMO in the study muddies the results but does not impact the way they interpret the overall study. The Panel is split on the issue of whether or not changing the grading scheme based on intubation had an impact on interpretability of that, with the folks that felt it did not was because it was applied to both groups, and those that think it did is

that without doing a full analysis, it's unclear to how patients shift across the PGD scoring to that end. So we continue to have mixed feelings in response to the questions.

DR. FISHER: Thank you.

DR. SCHWAITZBERG: Item 4 is a single question: The OCS Lung System did not demonstrate a survival benefit compared to control. Rather, an apparent risk of increased death in the early post-transplantation period seemed to be associated with the OCS device. Please comment on the clinical implications of the early OCS mortality, given the later equilibration of overall survival.

And we'll start with Dr. Hammon.

DR. HAMMON: If you look at this system of lines that's running diagonally across this page, you would say, well, this is about the same for both of them, probably not in the sense that the control patients started out better and ended up slightly better. But does that mean that the study was flawed? I would have to say no because these -- this kind of research often comes out in a very, very confusing way in the sense that you're trying to make something, you're really anxious to treat patients and have them live and enjoy a very fruitful life, and then you get something like this, and you wonder, well, what exactly did we do? Well, I think by this time, surely we know exactly what happened.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: So, frankly, I think that it's difficult to interpret the clinical significance of the early mortality. Typically, when you look at transplant survival as a gross approximation, if someone dies very early, it's the surgeon's fault, and if someone dies very late, it's the medical doctor's fault. And so looking at something like this, you have to think that, well, perhaps being on the OCS made it technically more challenging to do the operation, although that does not seem to be borne out in the rest of the data. So, you know, I think that the overall long-term outcome is obviously the one that we are most

concerned about, but I think that it is difficult to parse just from the data that we have what exactly that means.

DR. SCHWAITZBERG: Dr. Krupnick.

DR. KRUPNICK: Yeah, I agree with Dr. van Berkel. It's hard to make a comment on that; I don't know if it's powered enough. And with, again, a very complex process, I think we just have to look at whatever, 1-month survival, which is equivalent.

DR. SCHWAITZBERG: So not a factor in the way you'd interpret overall safety?

DR. KRUPNICK: That is correct. That is not a factor.

DR. SCHWAITZBERG: Mr. Stammers.

MR. STAMMERS: Al Stammers.

Yeah, I think we already talked about this in regards to perhaps the lack of ability of a 30-day mortality to accurately reflect an outcome here, so -- and the study investigators have shown that looking further out than 30 days mortality actually was not different, so this has no issue in my -- the way I interpret this.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: These Kaplan-Meier curves are remarkably interchangeable and, you know, any queries we have about the difference between them at 6 months is perhaps a post hoc approach to the data. It's not a pre-specified endpoint.

DR. SCHWAITZBERG: Thank you.

Dr. Connor.

DR. CONNOR: Yeah. I mean, while there is, you know, obviously a difference -- I've been hard on the Sponsor -- I would say I think that this is good that it bears out long term. I never understood why the primary endpoint was 30-day survival given these are oftentimes young patients who hopefully have many years ahead of them with a new set of lungs. So this is probably -- even if it's real, it's probably worth the tradeoff if it increases

the number of available harvestable and transplantable organs, though I think that's the key piece that we've been missing today is whether it really does increase the number of organs.

DR. SCHWAITZBERG: Mr. Thuramalla.

MR. THURAMALLA: I agree with Dr. Connor and Dr. Stammers's statements.

DR. SCHWAITZBERG: Thank you.

Mr. Frankel.

MR. FRANKEL: I would say that if someone showed this to a patient who has the option of standard of care, then yeah, I think that that would probably have a factor in their decision making as to which they'd prefer. There obviously could be limitations in this on a statistical level, I think that was just pointed out, but taking it on face value, I think, from the consumer's representative vantage point and looking at it for patients, I think that most patients would opt for the -- that blue line that they're following over there when they had the option between the two simply because of, you know, limited data or not. On face value it does appear that there's an advantage, again, for that patient that has the choice. For the patient that doesn't, obviously that's a completely different story.

DR. SCHWAITZBERG: Ms. Barnes.

MS. BARNES: You know, lung transplant patients obviously have a huge hurdle just because of their disease already, and then their chance of -- or their risk of death post-transplant for any reason is higher than other organs, as people have mentioned. I think, you know, if you -- if a patient chooses between -- if you give them the details and the information, they might be hesitant to choose the device if they knew that they would have a higher risk of death. However, considering that a lot of these patients, they're not really in this kind of situation, they're going to be transplanted anyway. Sometimes, you know, it could be the situation where a patient wouldn't be transplanted otherwise. And I think,

given that the availability of organs and the fact that these numbers are so close, that patients might choose to take that risk.

DR. SCHWAITZBERG: Thank you.

Dr. Moon.

DR. MOON: Yeah, I probably wouldn't show this curve to a patient because they wouldn't understand that those two curves are exactly the same, so I don't think there's any difference in survival between the groups.

DR. SCHWAITZBERG: Dr. Meyer.

DR. MEYER: I agree with the comments, no difference in survival.

DR. SCHWAITZBERG: Dr. Nathan.

DR. NATHAN: Whenever I see a survival curve, I'd like full representation with the y-axis going down to zero. Because it starts at 60%, so it makes the difference look greater than it actually is. And the 6-month survival still looks like it's more than 90%. And so I think you got to -- if you're going to show it to patients, you got to represent it in that context. But it does bother me a little bit when you see that difference initially, but the number of patients driving that, I think, was relatively small. The patients in the control group who died within 6 months, these are likely the patients -- it's not as if they were in retirement and were doing well and then drop dead. These are patients who are likely languishing in the hospital or in and out of the hospital with multiple problems who somehow got dragged through the first 6 months and eventually succumbed.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: Yeah, I also don't know how to interpret this. The y-axis is truncated, and it visually makes the graphs appear significantly differently -- different. If you look at the data, the short-term outcomes do appear to be different. And then I don't think we have a full understanding of the tradeoffs. We don't know non-survival type of long-term

outcomes, and so it's possible survivors in one group or the other may be worse off than the others.

And, again, I'd like to point out, this is a graph not of intention to treat but of modified intention to treat, so patients are missing from here. And, once again, the treatments were not blinded, and so, you know, I don't understand why this occurred early and who these different types of patients are, fully.

DR. SCHWAITZBERG: Would this be a factor in your overall approvability?

DR. YUSEN: Approvability?

DR. SCHWAITZBERG: For the device.

DR. YUSEN: This goes along with a theme, so yes.

DR. SCHWAITZBERG: Okay. Mr. Riley.

MR. RILEY: I believe the lines are similar and it doesn't affect --

DR. SCHWAITZBERG: Dr. Yuh.

DR. YUH: Yeah, I agree with many of the comments, that that's really too difficult to really separate the two, the curves from each other, in terms of any kind of conclusions or significance.

DR. SCHWAITZBERG: Dr. Afifi.

DR. AFIFI: If this were the total intent-to-treat sample, I would say the difference is not that big, although from a clinical point of view, from my point of view, early death, shown by the red line, would be a little more alarming than the other one. But because of the removal of a number of patients from the sample, it makes this even more difficult to interpret.

DR. SCHWAITZBERG: All right. Dr. Fisher, if I can summarize, the majority of the Panel felt that the early mortality would not be a significant factor in how they interpret the results. There is an additional opinion that due to the fact that patients were removed from

the study, it is not a complete intent-to-treat paradigm, but there is some concern about interpretability, but that is a minority opinion of the Panel. Does that answer your question?

DR. FISHER: Thank you.

DR. SCHWAITZBERG: We'll do Item 5, and after Item 5, I'm going to give Dr. Hassanein 2 minutes at the podium because he is dying to get up here --

(Laughter.)

DR. SCHWAITZBERG: -- but it will be -- but what I want -- because we have 10 questions, I'm trying to move through the pile.

(Off microphone comment.)

DR. SCHWAITZBERG: Perfect. Item 5: The safety endpoint was based on the average number of four pre-specified lung-graft serious related SAEs, per patient, up to 30 days following transplantation. The average number was 0.26 in the OCS arm compared to 0.29 in the standard of care arm. The treatment difference (OCS - SOC) was -0.031 with the upper one-sided 95% confidence interval of 0.06, which met the non-inferiority margin of 0.07.

Table is included for your review. Three items, please discuss all three.

a. Please discuss the appropriateness of the four pre-specified lung-graft related SAEs and the 30 day time point for assessing device safety, and the use of the average number of events as the primary safety endpoint.
b. Please comment on the clinical significance of increased incidence of respiratory failure in the OCS arm related to the risk of mortality.
c. Please comment on the clinical implications of the safety endpoint and its 4 components.

Since this is heavily laden as a statistical question, Dr. Connor, I will let you come to

bat first.

DR. CONNOR: I do not have any safety concerns.

DR. SCHWAITZBERG: Okay. Dr. O'Connor.

DR. O'CONNOR: All right, so for Question (a), "Please discuss the" --

DR. SCHWAITZBERG: Microphone.

DR. O'CONNOR: Sorry, please discuss the appropriateness of the four endpoints, the four endpoints are fine. I will confess that after hearing the study -- Sponsor's presentation and the FDA's discussion, I think they're insufficient. I would include rather than a 30-day endpoint for these, I think you should extend them to the initial hospitalization. One of these patients was in the hospital for 150 days after their transplant. So I think it would be fair to ask, for all of these, for the initial hospitalization or 30 days, whichever is longer. And, in fact, I would include the average ventilator days, the average ICU length of stay, and the average hospital length of stay as endpoints as well, in terms of safety endpoints, because somebody who spends 4 months in the hospital as a consequence of getting their procedure on one lung or the other is at substantial risk.

"Please comment on the clinical significance of the increased risk of respiratory failure in the OCS" limb, gosh, I'll defer to the rest of the Panel, but I mean, you know, it's of mild concern, but it's a relatively small bump.

"Please comment on the clinical implications of the safety endpoint and its 4 components." I've already kind of made it clear that I would prefer that we extend this to include the entire initial hospitalization.

DR. SCHWAITZBERG: Okay. Mr. Stammers.

MR. STAMMERS: The only thing I would add to this would be we're talking about device safety, and we really don't have any indicators in here looking at the individual device functionality from a mechanical perspective, so it would've been nice to perhaps use

that as a composite analysis as well.

As far as the respiratory problems that occurred in the OCS arm, I thought we discussed that in regards to not having a final determination of why that had occurred, but I don't know why that would be linked to the device itself. I don't have a feeling for that, so these don't bother me.

DR. SCHWAITZBERG: Sasha.

DR. KRUPNICK: Yeah, I'm not bothered by these at all, and respiratory failure is the only one that seems to have a high rate. And, again, in the absence of other factors, such as PGD, it's such a complicated factor to study in what is a small number of people, and I don't think you can make any conclusions, so I don't think this bothers me at all.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: I have no other comments.

DR. SCHWAITZBERG: Thank you.

Mr. Hammon, Dr. Hammon.

DR. HAMMON: I would be surprised if the safety endpoint was way down below what it is now in a group of patients this sick and in a situation where you are using -- clearly some of the people that we're treating, the patients had to grow up and use the device in question, the perfusion device. And so I think this is just something that is going to happen.

DR. SCHWAITZBERG: Okay. Dr. Afifi.

DR. AFIFI: No comment.

DR. SCHWAITZBERG: Dr. Yuh.

DR. YUH: Yeah, I don't have any quarrel with the selection of the safety endpoints. In terms of the respiratory failure, again, as the others, the numbers are relatively small, and I don't think I can attribute any proportion of that to failure of the device itself.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: No comment.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: I like the choice of the safety endpoints. I'm not -- other than I'm not sure acute rejection needs to be in there. I sort of view that as an efficacy outcome, but either way, it doesn't address things like antibody immediate rejection, donor-specific antibody type issues, which might be associated with blood being given with the solution, I don't know. It doesn't address pulmonary artery thrombosis, pulmonary vein stenosis, less common events that might be more impactful in a larger sample size, but overall, I think it was okay.

DR. SCHWAITZBERG: Dr. Nathan.

DR. NATHAN: I have no safety concerns. I like the endpoints they chose. These are some of the more common things that can happen in terms of respiratory failure, infection, specifically. I think the issue with the respiratory failure patients, without knowing for sure, is that these are probably the same patients who ended up dying, so we're seeing the same signal twice; it's just another way of getting at it. So I think I don't have any safety issues, concerns.

DR. SCHWAITZBERG: Dr. Meyer.

DR. MEYER: I think they all look like appropriate endpoints. The only question regarding respiratory failure, I'm not sure if -- and I doubt if this is true, but are there any issues with endothelial injury from the perfusion device or perhaps barotrauma from the device, even though, you know, they talk about how the lungs are wrapped to try to prevent this? So these are just two small things, but I'm not concerned about the safety, looking at these endpoints.

DR. SCHWAITZBERG: Okay, Dr. Moon.

DR. MOON: I don't have any safety concerns.

DR. SCHWAITZBERG: Ms. Barnes.

MS. BARNES: I don't have any safety concerns for the product. It always worries me when patients don't survive in this -- in a group like this, but I think, given the complexity of the disease and what's going on with them, I think that it's understandable. I can appreciate that it was a slightly lower infection rate and slightly lower acute rejection, and I think I heard that women might have done better in one area, so I'm for that.

DR. SCHWAITZBERG: Mr. Frankel.

MR. FRANKEL: I don't have anything in addition to add.

DR. SCHWAITZBERG: Mr. Thuramalla.

MR. THURAMALLA: No safety concerns based on the fact that the 30-day plus the in-hospital mortality was almost similar between the arms.

DR. SCHWAITZBERG: Thank you. So, Dr. Fisher, for the panel deliberations, the vast majority of the panelists did not have significant safety concerns. The majority felt that the endpoints were appropriate, although some panelists commented that they would've liked to have seen more data about the device, would've liked to have understood a little bit more about the histocompatibility, the release of potential factors. We know about the impact of blood on the immunology of, say, cancer outcomes, and none of these factors were studied. So there is a preference to have some more data, but there was not a general feeling that the endpoints were inappropriate or that there were really valuable endpoints that were missing. Does that answer your question?

DR. FISHER: Almost. So this is one of the few times that I will step outside the box and kind of move away from the study. Moving forward, okay, moving forward as FDA, I was wondering if any of the Panel members might have any suggestions on anything else that we should be collecting, moving forward. Some of you have provided some

suggestions, and I appreciate that, but I'm also just giving you an opportunity to say, oh yeah, you know, moving forward you should look at this. If you have not voiced them and would like to, I'd like to hear them.

DR. SCHWAITZBERG: So we've heard about some potential biochemical parameters that might've been interesting to study, discussing the potential effects of trauma to the endothelium.

DR. FISHER: Hospital stay. We talked about hospital stay.

DR. SCHWAITZBERG: Hospital stay.

DR. FISHER: Yeah.

DR. SCHWAITZBERG: Histocompatibility issues. Are there any other interesting data points that -- you know, device safety endpoints?

Mr. Stammers.

MR. STAMMERS: Al Stammers.

I would look at blood management. I think the fact that in this particular trial there may have been a diversity or a difference in the utilization of blood products, not only red cells but platelets and plasma having an effect, of course, on respiratory function would've been helpful, especially with an extracorporeal device, which we know changes how those systems are regulated.

DR. FISHER: Thank you. Any other suggestions?

MR. FRANKEL: If it would be possible to include, not on a clinical level, but as far as the patient is concerned, quality of life, because I think that there's a certain lapse of data in terms of what's exactly going on with these patients moving forward. So if it was able -- if we were able to see the difference in two arms of how the patients perceive themselves and how they're doing, I think that would be somewhat useful.

DR. SCHWAITZBERG: All right, the Panel Chair now invites Mr. Hassanein to come

make a comment.

DR. FISHER: We did have a hand.

DR. SCHWAITZBERG: Say again?

DR. FISHER: We did have one more --

DR. SCHWAITZBERG: Oh, I'm sorry.

MS. BARNES: Sorry, just one quick thing, and that is maybe some assessment of their ability to think the way they normally do or, you know, if there are changes based on --

DR. SCHWAITZBERG: Cognitive assessment?

MS. BARNES: Yes, thank you.

DR. FISHER: Great, thank you.

DR. SCHWAITZBERG: The Chair invites Dr. Hassanein to come up. A short comment.

DR. HASSANEIN: Thank you, Mr. Chairman. I promise to be brief. A 10-second comment to Dr. Yusen and Dr. O'Connor. We deeply regret the situation that we find ourselves in from the change in the protocol. We completely understand your concerns. To the rest of the panelists, I'd like to point out a few factual or just the factual statements about some of the statements that were made.

The one patient happened, and I say that with the deepest respect for all of our trial centers, it happened at the sites that had the highest rate of mortality in both groups. It happened at the site that had the highest rate of protocol violations in both groups. That particular patient was not changed after 2 years. That particular patient, from Day 1, the center never filled eligibility criteria, and it took a year with multiple queries to force the site to validate why that eligibility criteria was not filled. We take responsibility for not acting sooner, but it was not that TransMedics changed it later. So that's No. 1.

No. 2, the 30-day mortality, there hasn't been a single site-reported mortality, not in

a single CRF that is related to device malfunction. The 30-day mortality occurred because the patient overdosed on Coumadin at home, stroked out with an INR of 5.6. A patient at home that had an acute allergic reaction to immunosuppressive induction prior to the lung transplantation and suffers severe angioedema to the point that the transplant was almost cancelled and was given significant diuretics at home, 14 or 17 days later, at home, had a PE event. A patient that suffered intraoperative mortality because a new anesthesia resident in a Paris hospital administered clotting factors to an open ECMO circuit when the first lung was transplanted, with a P/F ratio obtained after the first lung greater than 300. There's one patient that could be attributed to a high-flow situation; it occurred in a center that a PI is represented here. That patient was re-transplanted and died. That death is counted in our study in the mITT population. However, that particular device issue was corrected since May 2013.

No. 2, the two device malfunctions that were excluded from the study, the protocol stipulates the definition for mITT analysis that needs to have harvested that is deemed eligible donor lungs. These two device malfunctions occurred before the retrieval team even left the hospital. This was not TransMedics or any member of our staff involved. The protocol stipulates what they are. We provided data to the review team, those patients survived, and I'm trying to get any data beyond the 30-day that we submitted already as a part of this PMA.

DR. SCHWAITZBERG: Last comment.

DR. HASSANEIN: The protocol ECMO. Both of them are alive at 24 month. Protocol ECMO did not occur in one center. That's a mis-factual statement. They occurred in six centers. They occurred three in the U.S., three outside of U.S. And, finally, the intubation and the PGD ECMO, we performed the sensitivity analysis, we provided this data, both of which did not alter the results of the primary effectiveness endpoint. There were eight

patients in each group, and as I suggested, we did both sensitivity analysis to the protocol ECMO, one censored and one taking them all as PGD3. It did not change the primary effectiveness endpoint.

Finally, the respiratory failure situation, remember that the OCS arm had higher IPH, secondary pulmonary hypertension, and -- yes, secondary pulmonary hypertension, IPH patient. We provided data in our core presentation to show that we followed those patients up to 24 months, and in hospital, 6 months, 12 months, and 24 months. The OCS arm, despite having slightly higher intubation rate, all those patients performed, survived better than control.

Thank you very much, Mr. Chairman, for recognizing me.

DR. FISHER: Excuse me.

DR. SCHWAITZBERG: Yes, Dr. Fisher.

DR. FISHER: A quick comment. So I can't comment on probably half of what you said because none of that information has been provided to FDA, okay? Now, I would've thought that some of that information would've been included in the PMA. It almost borderlines being inappropriate that we wait until the Panel to start bringing these things up when FDA hadn't had a chance to review it. So this wasn't meant to be summation, it's really meant to be a Panel discussion, and I would like to take it back there, please.

DR. SCHWAITZBERG: Right. So we'll go back to the questions. Thank you for the information, and thank you for the clarification, Dr. Fisher.

Going to Question 6 in the category of post hoc and adjunctive analyses: Although Bronchiolitis Obliterans Syndrome was not one of the safety endpoints, the protocol specified the accrual of data on the diagnosis of BOS at 6, 12 and 24 months. The inferences regarding BOS development are somewhat limited due to the unadjudicated nature of the data. TransMedics suggests a favorable decrease in BOS with the use of the

device. FDA failed to identify a clearly meaningful decrease in BOS at 24 months, and the rates of patient survival to 2 years without BOS appeared to be comparable between the two study arms.

Please discuss the significance of the BOS findings in relationship to the OCS system.

Why don't we start someplace where we haven't started before?

Dr. Yuh.

DR. YUH: Thank you very much. I think that the conclusion that there's a positive impact on BOS is premature, at best. I mean, the margin is razor thin, and to me, it's still a big leap to make from, you know, the purported effects of the device on primary graft dysfunction and BOS 2 years later. I just don't think there's enough data, I don't think the difference that you do show is particularly impressive, and so I think it's a big -- really, a bit of an overreach to make that conclusion.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: I agree with Dr. Yuh.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: Roger Yusen.

Same comments as before, caveats. I think it is very important, I'm not sure of the significance, but I would also add that I think CLAD, chronic lung allograft dysfunction, ought to be really the topic being addressed because there are many more patients that have chronic allograft dysfunction in addition to those with BOS.

DR. SCHWAITZBERG: Thank you.

Dr. Nathan.

DR. NATHAN: Yeah, I agree with Dr. Yuh and Dr. Yusen about using CLAD for future studies. I know there is this association between early perioperative events and PGD and BOS, but I'm concerned, and this might come into the 5-year plan, that, you know, it's very

hard to attribute what happens perioperatively to what happens 1 year, 2 years, 5 years down the road, and lung transplant recipients are so complex with so many different things that happen, I think we have to be very cautious about long-term dead and attributing to what happened in the perioperative period.

DR. SCHWAITZBERG: So were you sold on BOS reduction or not?

DR. NATHAN: I don't think there's a significant difference in BOS reduction. I agree with the FDA.

DR. SCHWAITZBERG: Thank you.

Dr. Meyer.

DR. MEYER: I agree with what has been said and how there's many factors related to BOS. I do think, going forward, again, getting back to that T0 PGD and following that versus following the other early PGD, like at 24, 48, 72 hours and relating that to BOS would be useful. But I don't think it really impacted on this study.

DR. SCHWAITZBERG: Dr. Moon.

DR. MOON: Yeah, I think there's a lot of studies that show that PGD does -- is related to BOS, but I think, looking at this study, the PGD rate was the same and the BOS rate is going to be the same.

DR. SCHWAITZBERG: Ms. Barnes.

MS. BARNES: I defer to the scientists.

DR. SCHWAITZBERG: Mr. Frankel.

MR. FRANKEL: I have nothing more to add.

DR. SCHWAITZBERG: Mr. Thuramalla.

MR. THURAMALLA: Nothing more to add. Thank you.

DR. SCHWAITZBERG: Dr. Connor.

DR. CONNOR: Yeah, the Sponsor Slide 84 uses the per-protocol, and it shows some

marginal benefit. I would focus more on the FDA slide, at least 169 in our pack, that uses the modified intent to treat but also does survival with freedom from BOS, which is probably more appropriate. That way, the patients who die aren't just censored. And there they seem to completely overlap.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: The rate of BOS in this trial is lower than in any of the reference studies that were cited in the manufacturer's presentation. And I don't believe there's any difference in the BOS rate.

DR. SCHWAITZBERG: Mr. Stammers.

MR. STAMMERS: No comment.

DR. SCHWAITZBERG: Dr. Krupnick.

DR. KRUPNICK: I don't think there's differences in BOS --

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: No additional comments.

DR. SCHWAITZBERG: Dr. Hammon.

DR. HAMMON: I agree, I don't think there's any difference in the BOS rate. I would like to address a short statement to the group sitting over here on my side behind the lectern, and that is, it's always really tough when you do something involving complicated analysis that doesn't come out the way you think it should have come out, and you just really have a hard time blaming yourself, and I'm not asking you to blame yourself. What I'm asking you to do is accept the fact that it didn't come out the way you thought it was going to and do better next time.

DR. SCHWAITZBERG: Thank you, Dr. Hammon. Very clever because he asked for the podium and I said no.

(Laughter.)

DR. SCHWAITZBERG: Dr. Afifi.

DR. AFIFI: I don't think there's any difference.

DR. SCHWAITZBERG: Thank you.

Dr. Fisher, the predominant sentiment of the Panel is that the claim that the device reduced bronchiolitis obliterans syndrome was not felt to be met, and that perhaps in future studies, since you're looking for input, that the use of the CLAD would be better or different or should be included in future long-term analyses. Does that answer your question?

DR. FISHER: Yes, it does. And a very quick comment: This is our only opportunity for us to be able to get the Panel's comments and your recommendations, okay? I can see the light at the end of the tunnel, we're almost there guys, okay, but that round was a whole lot of "no comments," and that's okay, maybe there weren't, okay, but we really need you to dig deep, okay, between now and the finish line, that if you have any comments or recommendations, this is when we need to get them from you guys, all right? Thank you.

DR. SCHWAITZBERG: I think that this particular question, that the answer seemed pretty clear.

DR. FISHER: No, I understand. I understand.

DR. SCHWAITZBERG: So I don't think it's a lack of commitment to the process.

Item 7: TransMedics seeks marketing approval for its device with the use of the OCS Lung Solution. TransMedics provided documentation indicating the OCS Lung Solution is equivalent to Perfadex. The INSPIRE pivotal study was conducted using both OCS Lung Solution and Perfadex. Please discuss the appropriateness of assessing safety and efficacy of the OCS Lung System based on the entire cohort of study subjects.

Before I go around the room, any questions about clarity of the question?

UNIDENTIFIED SPEAKERS: Yes.

DR. SCHWAITZBERG: Yes, I'm having the same problem. So, Dr. Fisher, can you boil the question a little bit for us? What is it that you really want to know?

DR. FISHER: So when we initially started the study, the study was done with Perfadex. There were some problems actually getting the Perfadex. The Sponsor came to us and petitioned to go ahead and be able to use the OCS lung solution, which they provided data to show that it was chemically equivalent, and FDA agreed. As we moved down, there was some suggestion that for marketing application, that they wanted to extend the study and they really just wanted to look at OCS lung solution patients, and we felt that since both solutions were chemically equivalent, that all patients should be included in the evaluation and not just one or the other.

DR. SCHWAITZBERG: Thank you. That adds clarity.

Why don't we start with Dr. van Berkel and work our way down your row.

DR. VAN BERKEL: So I think that it's appropriate to use both, especially if there is demonstrated chemical equivalence between the two. I understand that there is some anecdotal evidence that would suggest that the edema is worse with the Perfadex, but I would say in the absence of any actual clinical proof of that, that there is no real indication to separate the two.

DR. KRUPNICK: Yeah, I have no issues with using the OCS lung solution.

DR. SCHWAITZBERG: Did you think it was different than the Perfadex?

DR. KRUPNICK: Well, the anecdotal data that they showed said it was a little improved over Perfadex, but we don't have the hard data. I mean, I don't remember being convinced by any data that's improved.

DR. SCHWAITZBERG: So we should be looking at the totality of the data?

DR. KRUPNICK: That is correct.

DR. SCHWAITZBERG: Thank you.

MR. STAMMERS: I agree. I think, from a chemical constituent perspective, there's loads of research models that are out there that could look at the two solutions and in ex vivo preparations, to have shown if there was some risk with endothelial leakage and edema occurring with one or the other, but the fact that these are the same chemical constituents -- we use cardioplegia that are the same in, you know, hundreds of different cardiac centers and don't anticipate differences.

The only thing I would answer your question with, it would be that I don't know why they just didn't continue with the randomization of both. I know you said that there was some restriction in Perfadex, getting the solution, compared solution, but it just seems like it was a late arm to throw. And then when we saw the statistical analysis with the graphs with just the OCS solution, you know, that didn't make much sense to me, why it couldn't have a separate arm with the competitor's solution as well.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: So, first of all, this question is not about a pre-specified endpoint in the protocol. The second is that, if my understanding is correct, if they started with the Perfadex and then switched to the OCS lung solution, my problem with that is this, and that is that outcomes get better over time. Anything that you did more at the beginning of any study and less at the end of any study would be associated with worse outcomes over time. And so I would argue that the way that this study should be analyzed is using Perfadex and OCS solutions interchangeably.

DR. SCHWAITZBERG: So totality of the study should be considered?

DR. O'CONNOR: Yes.

DR. SCHWAITZBERG: Thank you.

Dr. Connor.

DR. CONNOR: Yeah, I think that's a key point. I totally believe it's appropriate to use all, and I think that the fact that we were discussing this is a bit of evidence that just the Sponsor was looking at data throughout, thought they even saw something different and wanted to discuss changing the analysis or whatever in terms of what looks better, which -- I'll leave it at that.

DR. SCHWAITZBERG: Mr. Thuramalla.

MR. THURAMALLA: I agree with the Panel. The totality of the data should be considered, but I would like to also add that down the line, during the future studies, if the differences between the OCS lung solution and Perfadex become more prominent or significant, a very deep and a thorough root cause analysis should be done to understand what is the source of these problems to make sure those don't happen in real life.

DR. SCHWAITZBERG: Mr. Frankel.

MR. FRANKEL: I think it's very difficult to argue against looking at it in its totality simply because the Sponsor wasn't able to propose any tangible reason why there would be any difference between those two, and the FDA, it seems, had prepared quite extensively to explain how they didn't find there to be any contrast between those two. And without any type of tangible evidence that there is a difference between the two, I think that it should be looked at in its totality.

DR. SCHWAITZBERG: Ms. Barnes.

MS. BARNES: I agree with Dr. O'Connor.

DR. SCHWAITZBERG: All right, Dr. Moon.

DR. MOON: Yeah, I don't think we -- I think we should look at it all in its totality, and if they want to do a subanalysis later, I think they'd have to get another control group or pick a select control group and not use the whole series, because time has a significant impact on the outcomes, I think, like Dr. Connor said.

DR. SCHWAITZBERG: Do you think the data supports unique labeling only using the unique OCS lung solution?

DR. MOON: No.

DR. SCHWAITZBERG: Okay. Dr. Meyer.

DR. MEYER: I agree with looking at the data in totality, and it would be good to see, in a side-by-side comparison, the chemical constituency of the two solutions because they are supposedly identical, but for some reason there was some, you know, anecdotal difference, but in totality.

DR. SCHWAITZBERG: Thank you.

Dr. Nathan.

DR. NATHAN: I agree that we should look at it in its totality, and I think the plan should be if the device is approved, then it should -- the difference can be captured in a database that's kept, I think it was mentioned over on that side, and I think we'll get the answer in the future.

DR. SCHWAITZBERG: Does the data support only approvability of the OCS lung solution?

DR. NATHAN: No.

DR. SCHWAITZBERG: Okay.

DR. NATHAN: Both together.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: I think the entire cohort should be looked at. This is a subgroup analysis with the same caveat as before. I think if this is a really important issue, you know, a factorial design, trial and device solution, you know, could be considered, but that wasn't done here.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: Dr. O'Connor made a very good point, and I agree with him. You know, me digging deep is -- would be to add osmolarity and oncotic pressure to the factors that we're going to measure in these organ preservation systems. And you wonder if the respiratory, the difference in the respiratory failure number had something to do with the ability to control osmolarity during the perfusion part. But I agree that it should be combined together, and I'd like to know if the osmolarity is one of those chemical factors that was dissimilar.

DR. SCHWAITZBERG: Fair enough.

Dr. Yuh.

DR. YUH: Yes, based on the chemical equivalence, I agree with the majority that assessing the whole cohort in its entirety is appropriate.

DR. SCHWAITZBERG: Dr. Afifi.

DR. AFIFI: I agree, the entire cohort should be used.

DR. SCHWAITZBERG: Dr. Hammon.

DR. HAMMON: If, in fact, the two solutions are exactly the same, I would agree to study the whole OCS group as a whole in the entire study. However, if there is any suggestion that there are some differences, try and figure out what it is, and then you can try and randomize the two later.

DR. SCHWAITZBERG: So, Dr. Fisher, the group did achieve consensus that the totality of the data should be looked at when queried. The panelists, when queried, felt that approvability should be based on both solutions and that there isn't sufficient data to suggest that approval should be -- just include one solution.

DR. FISHER: Thank you very much.

DR. SCHWAITZBERG: Question No. 8, post-approval study section: The primary effectiveness endpoint in the new enrollment Post Approval Study (PAS) is 5-year survival.

TransMedics proposes to conduct a hypothesis test to demonstrate that 5-year survival in this PAS is greater than 38.4% (performance goal of 50.4% with a 12% margin). The survival rate of 50.4% was based on Organ Procurement and Transplantation Network data of double-lung transplants between 1997 and 2004.

A 2015 annual report from OPTN reported a 5-year patient survival rate of approximately 60% in patients who underwent double-lung transplantation between 2008 and 2010. Based on these data, FDA recommends that a point estimate of 60% is more appropriate for the PAS.

Please discuss what would be an acceptable point estimate to which 5-year survival in this PAS cohort should be compared, and what would be an acceptable margin that will not be clinically different from the point estimate.

So I'm going to -- Ms. Barnes, I'm going to start with you. I know this is kind of a statistical thing, but you get to go first.

MS. BARNES: Yes, thank you for asking. I would defer to the scientists on the point estimates, but I would, you know, encourage also taking a look at single-lung transplants as well, down the road.

DR. SCHWAITZBERG: Okay. Mr. Frankel.

MR. FRANKEL: Yes, I think that it would make sense to go in accordance with the updated data, which I think was 55.5% rather than 60, but to utilize that as a base point rather than the out-of-date data.

DR. SCHWAITZBERG: You want to comment on the margin?

MR. FRANKEL: I don't have anything to add to that. I'll leave that to the statisticians.

DR. SCHWAITZBERG: Tough question.

Mr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla.

I'll defer the question to the statisticians, but I'd like to just add, for the post-approval study, we should follow the 2016 consensus statement and therefore consider adding the PGD3 at T48 also.

DR. SCHWAITZBERG: Okay. This is a statistical question, so Dr. Connor.

DR. CONNOR: Yes. So I agree, this actually illustrates Dr. O'Connor's point very well that things get better over time, so using more recent data is absolutely appropriate. I would question -- I'm not an expert in the UNOS database, but I wonder if there's sufficient granularity there that we could actually use concurrent controls and pre-specified concurrent controls, given that I think all of these patients in the U.S. are tracked, so I would consider that.

Regarding the margin, I think that that is a question that I would feel comfortable that FDA negotiates. As they said earlier, depending upon where the value is, a margin should be smaller if it's closer to zero or one and can be bigger in the middle due to statistical artifacts and such. So I think the margin of 10% or less negotiated by FDA would be fine.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: So I'm going to say that I believe that the approval of this device could actually produce an increase in transplants in higher-risk patients with longer ischemic times and therefore, perhaps, even a decline in the 5-year survivorship associated with an increased number of transplantations. And so I'm hesitant to invoke even 2008 to 2010 5-year survivorships. What I would do instead is have them pre-specify a risk-adjusted survivorship. So, for example, if they were using this on exactly the same kinds of patients that are in the 2008 to 2010 report, they should be able to hit a 60% target for survivorship.

But if they're out there taking the risks -- and they're going to be; that's what they're going to use this device for. It's reasonable to speculate that even outcome equipoise

would represent an improvement, right, and it's possible that even worse outcomes might be, in aggregate, better for the patient of lung transplant -- population of potential lung transplant recipients. So I favor a risk-adjusted, utilization-adjusted evaluation of the device compared to the 2008 to 2010 baseline.

DR. SCHWAITZBERG: Thank you, very insightful.

Mr. Stammers.

MR. STAMMERS: This is registry data, and it just seems that, you know, even looking at 7-year-old data, that that's antiquated, and I think that there have been a lot of changes and advances even in the last decade that need to be taken into consideration. So I would recommend that 60% seems to be adequate, but these numbers are well known, and they should be discoverable, and to use the most recent data when the submission occurs.

DR. SCHWAITZBERG: Dr. Krupnick.

DR. KRUPNICK: So I'm a little confused. The fact that now in this study there will be no control group, so we have to use some sort of a historical control, is that the main question?

DR. SCHWAITZBERG: Right, they have to pick a point --

DR. KRUPNICK: Got it.

DR. SCHWAITZBERG: -- analysis.

DR. KRUPNICK: Got it, got it. Yeah, so I kind of agree with Mr. Stammers, that I think we have to use the last data for 5-year survival available, although knowing that, you know, the 5-year survival is going to go up just based on improved care of these patients, so 60% seems more reasonable than 50.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: Yeah, so there absolutely is granularity within the database to be able to pick and choose however we want to do this. We could be as fancy as we want or

we can do propensity matching. You could do -- you know, you could try to do risk adjustment in that regard, and so I think yes, you could pick a much more rigorous control group essentially.

DR. SCHWAITZBERG: Dr. Hammon.

DR. HAMMON: I can't imagine that the overall survival is going to go down below 60%, but since we need to have a margin, I would say put 3% on either side.

DR. SCHWAITZBERG: Pretty tight margin.

Dr. Afifi.

DR. AFIFI: I think the most recent data should be used, and I very much agree with Dr. O'Connor about a risk-adjusted survival rate. That would be more appropriate.

DR. SCHWAITZBERG: Dr. Yuh.

DR. YUH: I like Dr. O'Connor's risk-adjusted concept, but if you have to pin me down on a number, I would probably pick something on the order of 50, 55% with a 5% margin. Fifty-five percent seems to be, at least, not the most recent data, but seems to be more of a consensus aggregate data over a longer time period.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: Jeff Riley.

I have nothing to add to this conversation.

DR. SCHWAITZBERG: Thank you.

Dr. Yusen.

DR. YUSEN: Roger Yusen.

I couldn't give a specific number. I do have concerns about secular trends. I agree with some kind of a risk adjustment, and the comment about that more sicker patients might get transplanted, it might change mortality, I think the whole control group issue is the most important thing.

DR. SCHWAITZBERG: Dr. Nathan.

DR. NATHAN: I agree. I don't think the '97 to 2000 for comparison is appropriate; that's before the inception of the current allocation score system, and we're transplanting very different patients now, many more COPD patients and more ILD patients now. So think about at 2017 we should have 5-year survival data on anyone transplanted in 2012 and previously, so I think a more recent comparison is in order. I'm not sure what the right number is. I think 55% seems reasonable.

However, I'll allude to some -- I'll talk about something that I alluded to earlier in that we're not accounting for the gain on the front end of transplant. In other words, if we are able to offer 5% more patients opportunity to be transplanted and we need to account for that on the back end, so there might be patients who wouldn't be transplanted without the system, so if we say it's 5% more, then maybe we should forgive another 5% on the back end because of that increased gain in patients who have the opportunity to get transplanted.

DR. SCHWAITZBERG: Dr. Meyer.

DR. MEYER: I agree with the more recent data, but I would go more with the 55% 5-year survival based on what was said before, that it could be a sicker group of patients that we will -- that will be, you know, utilizing this technology.

DR. SCHWAITZBERG: Dr. Moon.

DR. MOON: It's a little unclear to me why we can't just use the control group that we just created and their 5-year survival as the target because, I mean, that's going to be the most recent study group. It's going to have 160 patients in it, and we're going to know their 5 years before the PAS 5-year survival data comes out.

DR. SCHWAITZBERG: To clarify, those patients are going to be followed regardless.

DR. MOON: Right, exactly. But I mean --

DR. SCHWAITZBERG: This is for the new patient -- new patients that have be entered into PAS.

DR. MOON: Right, but I think they should be compared to this new control group. I don't know. It doesn't make any sense to me why we can't -- why we have to pick a number right now for the PAS, which isn't going to be done for the next 5 years plus.

DR. SCHWAITZBERG: All right, Dr. Fisher. The majority of the Panel felt that using more updated data is appropriate. There is some mixed feelings about the potential for improvement of transplantation science versus the impact of transplanting sicker patients, so many panelists felt that using some sort of scoring severity risk adjustment would be appropriate to understand the outcome of the device in its best. So, to summarize, more recent data with severity scoring adjustment.

DR. FISHER: Any comments on the performance goal?

DR. SCHWAITZBERG: Any further comments?

DR. FISHER: I did hear some comments higher than what was here. Is the Panel in agreement there?

DR. SCHWAITZBERG: So there were some panelists who felt that the performance goal could be as low as 3%, 5%, and some were satisfied. One said 12%. So the margin scores were really all over the map without clear consensus.

DR. FISHER: Okay, thank you.

DR. SCHWAITZBERG: All right. Item 9: TransMedics proposes to collect data on the following additional endpoints: short-term and long-term survival; PGD Grade 3 within 72 hours post lung transplantation; and long-term assessment of BOS.

Remember, this is in the context of post-approval studies.

While FDA supports the collection of PGD data at all key time points up to and including 72 hours, FDA recommends that PGD3 outcome assessment is based on 72 hours.

Please discuss the appropriateness of the proposed outcomes and the follow-up assessment in order to evaluate the short-term and long-term safety and efficacy of the device.

So, to clarify, FDA is proposing PGD3 at 72 hours versus PGD data at all key time points. Why don't we start with Dr. Nathan.

DR. NATHAN: I agree with the FDA to do it at 72 hours. I think, in terms of the clinical study, doing it at T0 increased the event rates, and maybe that's some justification for using T0, but I think PGD at 72 hours is more relevant, and I think that might also help with all the issues of ECMO in terms of patients, hopefully, should be off ECMO around that time, so I think the 72-hour time frame is reasonable. What else? I think it's mostly about PGD.

DR. SCHWAITZBERG: Thank you.

Dr. Meyer.

DR. MEYER: I agree the 72-hour time point is probably a good one, although ensuring that all the other data points do get collected and analyzed as well.

DR. SCHWAITZBERG: Dr. Moon.

DR. MOON: It's an incredibly simple statistical thing to do the outcome assessment at every time point that you collect the data, so just do it at every time point.

DR. SCHWAITZBERG: Ms. Barnes.

MS. BARNES: I agree with Dr. Moon.

DR. SCHWAITZBERG: Mr. Frankel.

MR. FRANKEL: I think also that it should be collected at both points, at least by T0 as well as 72, but I think the additional data may be useful at a later point, but during analysis.

DR. SCHWAITZBERG: Mr. Thuramalla.

MR. THURAMALLA: So I'd like to repeat the same thing as I said before, that is, being consistent with the 2016 consensus statement, which says PGD3 present at T48 and T72

appears to have the greatest impact on the long-term outcomes, including BOS and mortality. So, for that reason, I would say it should also include PGD3 analysis at T48 in addition to T72.

DR. SCHWAITZBERG: Thank you.

DR. CONNOR: Yeah, I would mainly defer to the clinicians, but I think that's the key point, that really this is an early biomarker predicting something that occurs later. The risk we've seen today is that, you know, one at zero is equally weighted as a death, which is crazy. So I think just measuring it at all times is fine, but applying the appropriate weight during the analysis, whether formally or informally, is the key.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: DR. GUD, I listened to what you said earlier. So I'm going to say that I think they should get PGD at T0, 24, 48, and 72. I think that other short-term outcomes for them should be ventilator days, ICU length of stay, hospital length of stay. I think that they should look at their safety endpoint, respiratory failure, infection, rejection at both 30 days or initial hospitalization, whichever is longer. I think we should ask them to evaluate functional status of recipients at 6, 12, 24, 48, and 60 months because I think that matters. Once again, if all these things -- and finally, they should have BOS-free survivorship at each of those intervals.

DR. SCHWAITZBERG: Thank you.

Mr. Stammers.

MR. STAMMERS: I think collecting the data is reasonable, but choosing an endpoint for a single-point assessment or at least as a secondary assessment, PGD3 at 72 hours is very reasonable.

DR. SCHWAITZBERG: Go ahead.

DR. O'CONNOR: I forgot one, and that is I'd like them to have a consensus definition

of BOS across their sites, preferably something along the lines of what Dr. Nathan described earlier, which is their new baseline functional status.

DR. SCHWAITZBERG: Thank you.

Dr. Krupnick.

DR. KRUPNICK: On this point, I'm going to agree with Dr. Moon.

DR. SCHWAITZBERG: Okay.

DR. VAN BERKEL: I think that looking at PGD Grade 3 within 72 hours is reasonable, with the caveat that, especially if the 2016 consensus statement that comes out is expected to be what we all think that it's going to be, that they're going to say that looking at T0 is complicated because there are too many variables in how its interpreted, and as such, I would say that T0 should be eliminated from that. I think that there is data that suggests that earlier time points like 24 and 48 are beneficial but that that T0 has too many confounders, and there's too many things that can make you think that there's a problem when there isn't actually a problem. And so based on what the upcoming recommendations are, I would alter my enthusiasm for having T0 in there.

DR. SCHWAITZBERG: So you're more of a fan of 48 than 72?

DR. VAN BERKEL: Yes.

DR. SCHWAITZBERG: Dr. Hammon.

DR. HAMMON: I agree with Dr. O'Connor.

DR. SCHWAITZBERG: Dr. Afifi.

DR. AFIFI: From a clinical point of view, it seems that 72 hours, at 72 hours is good enough, but from a statistical viewpoint, since we have all the data, I would look for some sort of a weighted average of the information at all time points.

DR. SCHWAITZBERG: Dr. Yuh.

DR. YUH: I would lean toward analysis centered around the 48- and 72-hour marks,

and I certainly agree with all the additional parameters that Dr. O'Connor listed and probably also add a supplemental oxygen dependence and duration thereof as well.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: Thank you. Jeff Riley.

I agree with Dr. O'Connor, and I think we should follow the guidance document like Dr. Connor said, as our guide for this. The challenge with length-of-stay data and like the time on the ventilators is everybody doesn't share the same protocols for removing patients, so we'd have to watch that there's some shared mental model or protocol for those types of data.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: As usual, I have a complicated answer; I'll try to make it brief and try to make sense. I think the early PGD grades -- T0, T24 -- might have important short-term outcomes. I agree that the T48, T72 time points would be more predictive of long-term outcomes. I do think PGD2 and 3 based on data may be prognostic, and one might consider lumping those two together as well as looking at 3 by itself, and I think somewhat ignored is the trajectory of PGD. Those who have persistent high scores, you know, there's many things that could be evaluated here. So I would propose that many different things be evaluated. In addition, other than the PGD issue are the long-term outcomes. And, again, Dr. Nathan and I were just chatting, I agree with looking at BOS. There was a mention of looking at UNOS data. Problems might exist with the recording of BOS data where you don't get a date, you get a yes or no within the reporting 1-year time period in the long run. That may be problematic.

In addition, there's not standardized collection of CLAD data. So, again, I would propose that this ought to be site-specific CLAD data collection potentially with subgroups such as BOS.

Related to that, I think it's important to look at time to the development of these things, and thus if those kind of models are being developed, I think there ought to be clear rules on dealing with competing events such as re-transplant.

And then, finally, because there are so many deaths, speaking about competing events, I think it would be important to look at CLAD-free survival and BOS-free survival. So I think there's a lot of things that ought to be looked at, and I think they're all important.

DR. SCHWAITZBERG: Thank you.

Dr. Nathan.

DR. NATHAN: My comments -- but I agree with what Dr. Yusen said, and I also agree with what Dr. O'Connor said. I think there should be a way towards early outcomes in terms of intubation, time in the hospital, ICU length of stay, because I think that's where PGD has most of its effects with probably lesser influence on BOS down the road, and CLAD being important as well. That's chronic lung allograft dysfunction for those of you who don't know.

DR. SCHWAITZBERG: Are all PGD time points equal, or do you have a weight?

DR. NATHAN: No, I think T72 is most important. It's not to say don't collect T24 and T48, but I think T72 is the most important for long-term outcome.

DR. SCHWAITZBERG: Dr. Meyer.

DR. MEYER: I already commented.

DR. SCHWAITZBERG: Oh, you started. Thank you. All right. Do you want to go again?

(Laughter.)

DR. SCHWAITZBERG: All right.

(Off microphone comment.)

DR. SCHWAITZBERG: Dr. Fisher, in this complex topic, the majority of the Panel felt

that PGD should be collected at all time points. There was a preponderance of weighting of the T72 as well as the T48 as primary endpoints, but there was an opinion that there would be some value in looking at the earlier PGD endpoints for perhaps short-term impact. But there was general consensus that the most important time points were the T72 and T48.

DR. FISHER: Thank you very much.

DR. SCHWAITZBERG: In addition, just one last thing, there is a plea to look at these PGD scores in relationship to vent days, SICU days, total hospital days, BOS with the need to tighten down the definition, ventilator status and performance.

DR. FISHER: Thank you for that additional.

DR. SCHWAITZBERG: All right, Item 10: TransMedics did not specify a primary safety endpoint for the new enrollment PAS. FDA recommends that the incidence of lung graft-related adverse events up to 90 days or more post-transplant is a clinically meaningful measure. FDA recommends these events include acute rejection, respiratory failure, infection, and bronchial anastomotic complications. Please discuss an appropriate primary safety outcome, including time period and acceptable margin.

So I will start with -- who hasn't had a chance to start? Dr. Krupnick. And we'll go this way.

DR. KRUPNICK: So, looking at this, I don't think acute rejection can fairly be on this graph because while PGD, for example, does modify acute rejection, it has so many factors based on pre-sensitization, donor graft, patient mismatch that I think would be impossible to control. Ninety days seems a little too long because if you're looking at adverse events related to organ preservation and immediate perioperative outcomes, it seems that 90 days might not be that useful.

You know, respiratory failure, infections, sure. Bronchial anastomotic complications which are related to PGD are now some of the technical issues, maybe with placing the graft

on the machine versus cold preservation, those kind of make sense. You know, there can be other, I suppose -- other aspects that might be indirectly related to this, you know, such as pulmonary embolism or some other complications, but I don't think acute rejection should be on this.

DR. SCHWAITZBERG: If 90 days is too long, since they're looking for a time period and a margin --

DR. KRUPNICK: Thirty days.

DR. SCHWAITZBERG: So you'd like to stay with 30, 30 days or 30 days -- or hospitalization, whichever's longer?

DR. KRUPNICK: Oh, correct. Thirty days or hospitalization, that is correct. Correct.

DR. SCHWAITZBERG: Mr. Stammers.

MR. STAMMERS: Yes, I'm going to defer to the pulmonologists and surgeons in the room because I really don't know what an adequate time would be in regards to postoperative follow-up, but I agree with Dr. Krupnick, what he just mentioned. And I assume these are composite safety measures; is that what they were?

DR. SCHWAITZBERG: Yeah.

MR. STAMMERS: Okay. So I think that's reasonable.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: So I agree with including all of these as endpoints. I think they're great. I would, as well, accumulate them once again for initial hospitalization or 30 days, whichever is longer. And I guess the one thing I would add to this, right, is that once again, if they believe they're going to reduce vent days, ICU days, and hospital length of stay, the other one I want is functional status at discharge and discharge destination.

DR. SCHWAITZBERG: Dr. Connor.

DR. CONNOR: I would agree that they should have pre-specified safety endpoints

and leave the rest up to the clinicians.

DR. SCHWAITZBERG: Mr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla.

I agree with Dr. Krupnick, that is 30 days or hospitalization, whichever is longer.

DR. SCHWAITZBERG: Okay. Mr. Frankel.

MR. FRANKEL: I agree with these recommendations from the FDA as well as the additions that Dr. O'Connor noted.

DR. SCHWAITZBERG: Ms. Barnes.

MS. BARNES: And I would defer to the scientists.

DR. SCHWAITZBERG: All right, Dr. Moon.

DR. MOON: Yeah. I like the list, again, without acute rejection. I'm not so sold on ventilation days and ICU days and length of stay days and that kind of stuff. I think that too many other factors go into that, and it's -- I think these hard endpoints are more important, at 30 days or in hospital.

DR. MEYER: I agree with those comments as we're really focusing on safety, so the 30 days or hospitalization with these endpoints.

DR. SCHWAITZBERG: Okay.

DR. NATHAN: I agree with my colleagues to the left, 30 days, and these are reasonable endpoints to monitor for, for safety.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: Pretty much agree. Would just like to reiterate the thrombosis issue might be important and then the antibody-related issues.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: Nothing to add.

DR. YUH: I agree with the 30-day interval. I think despite the multifactorial factors

that go into acute rejection, I think I would still like to have that information and include that as an endpoint.

DR. SCHWAITZBERG: Dr. Afifi.

DR. AFIFI: I defer to the clinicians.

DR. SCHWAITZBERG: Dr. Hammon.

DR. HAMMON: I agree with 30 days. I think you ought to put acute respiratory or just respiratory failure first on the list but include acute rejection; after all, this is transplantation.

DR. SCHWAITZBERG: Thirty days pure, or 30 days or hospitalization?

DR. HAMMON: Or hospitalization.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: No, I don't have any other comments.

DR. SCHWAITZBERG: Great. Dr. Fisher, the Panel generally felt that the endpoints that were suggested were good endpoints. There were some panelists who did not -- were not as excited about things like acute rejection, felt that 90 days was probably too long, that 30-day mortality or hospitalization, whichever is longer, is a better endpoint, and suggested looking at some other factors such as functional status at discharge and other issues such as thrombosis. Does that answer your question?

DR. FISHER: Yes, thank you very much.

DR. SCHWAITZBERG: I would like to, before we go to summation, thank all the panelists for their comments. This is very -- a very complicated study, a lot of complex issues concerning the fact that parameters changed during the study, and I'd like to thank everybody for a very thoughtful discussion of the issues.

We'll now go into summations. The Sponsor will get to go first. You get 10 minutes, but I'm going to cut you off at exactly 10 minutes if you're not done sooner.

DR. ARDEHALI: Hopefully it would be much less.

DR. SCHWAITZBERG: There you go.

DR. ARDEHALI: Thank you. Once again, I'm Abbas Ardehali, one of the lung transplant surgeons from UCLA. I want to close this presentation by taking a step away from all the questions and issues that we've discussed throughout the day and in the afternoon and focus on what really matters: patients. Let's not forget why we're all here and why I'm here today, and that reason is the patients.

Lung transplantation is a lifesaving procedure. Sometimes we forget how amazing it is that we actually take two lungs out of a brain-dead donor, transport them halfway across the country, and implant them into a sick recipient to save their lives. These donor lungs are incredible lifesaving gifts, and what we do with them right now is to preserve and protect that gift in a bag of ice in an Igloo cooler. Obviously, this approach is extremely limited. We cannot assess these lungs, we cannot monitor them, we cannot optimize them, and we cannot protect them from ischemic injury. And this is what we have lived with for the past 30 years. And today, with your support, we may be able to change that.

We have known for years that ex vivo lung perfusion, preserving donors in a near physiologic state outside of the body, is the future of lung transplantation. What we have been looking at today is the largest study ever conducted in surgical lung transplantation, and the data demonstrate that the future has arrived.

One thing we all have discovered by now is that this trial had many issues: There were imbalances in the protocol deviations, imbalances in the screen failures, and there were changes in the design of the study. This is far from ideal. These learnings must be recognized, acknowledged, and avoided in the future trials. But what we need to keep in mind is that this trial was an incredibly complicated investigation. This is the first randomized trial ever conducted in lung preservation.

I want to acknowledge and thank all the 21 lung transplant centers, the PIs, and the staff, who helped us to complete such a monumental study. It took over 2 years to design and negotiate the initial study with the FDA, and I'm not going to sugarcoat this; the fact is that there were disagreements from step one on the best way to assess the effectiveness of this technology. As an independent academic clinician, I want to say that everything from the steering committee's perspective that has been done has been done in the best interest of the patients, with the sole intent in generating the most clinically relevant data for lung transplantation and preservation technology.

These issues aside, the data are the data. You have seen it throughout the day. And when you look at the data in the totality, you see a clear picture. First, the device is clearly safe. This study met its safety endpoint. Early mortality was nearly the same, including the hospital, was as control. Lung graft-related serious adverse events and the survival rate at 2 years was almost identical to the control group. The only difference in safety that may or may not be statistically significant was that there was a trend towards lower BOS in the OCS group.

The second finding is that the device is effective. Regardless of the way you look at the PGD, whether at 72, within 72, or other time points, the OCS is either similar or better than control when it comes to the incidence of PGD3. This is the first medical technology to reduce the incidence of PGD3 ever. The patients who received lungs on the OCS had shorter ventilation times, shorter lengths of ICU stay, and the hospital stay. The device decreased the amount of time for ischemic preservation of the donor lungs. This device allowed the clinicians to keep donor lungs preserved longer. The majority of the data is either significant or trending in the favorable direction for the OCS.

So while INSPIRE was not a perfect trial, and I think everyone agrees with that on the part of the steering committee, I think it has demonstrated that the OCS system will deliver

clinical benefits to patients without additional risk. And in the end, that is what matters the most. It has met the standard for approval. It is safe, it's effective, and its benefits outweigh its risks.

We have a long way to go to unleash the full potential and capabilities of this platform. Approval of this first indication will be the catalyst that's needed for these future ongoing studies. I respectfully ask the Panel for your support to allow the lung transplant community in the United States to have access to this technology and take the next step and continue to improve this area. Thank you.

DR. SCHWAITZBERG: Thank you very much.

We'll take summary comments from the FDA.

DR. FISHER: Well, thank you. First, I would like to thank TransMedics for their presentations and participation today, and I'd also like to thank the members of the Panel for their participation and their insightful discussions this afternoon.

There's been some points of disagreement discussed today, but here are the undisputed facts: 15% of the patients on the lung transplant waiting list die waiting for an acceptable donor organ, and only 20% of the available donor lungs are actually used for transplant.

So the first modernization of lung transport devices was developed in the mid-1980s, and it consisted of flushing a lung with a cold perfusion solution and storing and transporting the donor lung in essentially an ice chest, right? And as simple as this system may seem, it still remains the standard of care method today.

So let's fast-forward 25 years, and we have developed machines that are much more sophisticated, and they're capable of continuous perfusion and ventilation of a donor lung during storage and transport. These machines can perfuse the donor lung at any temperature ranging from standard cold temperatures to normal physiological

temperatures, and they have a capacity to measure a number of physiological parameters. Questions still remain about the validity of these physiological parameters as key measures when assessing the donor lung for transplant.

Now, logically one might assume that a donor lung treated and transported in one of these new machines would fare as well as one stored and transported under current standard of care methods, but FDA cannot simply use blind faith as part of the regulatory decision process. We must continue to use valid scientific evidence.

So, in the case of a PMA, what does FDA expect to see? Well, while not an absolute requirement, the ideal study would be a randomized clinical trial. It would be one with pre-specified endpoints, one statistically powered for hypothesis testing, one with inclusion and exclusion criteria that selects for appropriate patient populations to test against the indication for use, and one that controls for patient safety while minimizing variability and bias.

So there's been discussion today regarding the primary endpoints. So where does FDA get the recommendations for its primary endpoints? I want to say up front that FDA does not develop the primary endpoints. FDA bases its recommendation for endpoints and the criteria for scoring these endpoints on positions developed by professional societies and the available supportive clinical literature at the time of the development of the clinical protocol.

Now, is it possible that within 3 to 5 years that it takes to conduct a clinical trial, that there might be changes in the practice of medicine? Well, that's possible, but if it doesn't impact the patient safety, then the clinical trial should follow the path outlined in the original clinical protocol.

You heard this morning that FDA is restricted in our ability to disapprove an IDE or changes in ongoing clinical protocols. So regardless of how the data is being monitored

during the conduct of a trial, if a sponsor chooses to change their primary endpoint while the trial is ongoing, and if that change does not affect patient safety, FDA is limited to disagreeing with the sponsor, and in our response letter, FDA warns the sponsor that the changes made during the conduct of the study might impact the validity of the data interpretation.

Now, does that mean that FDA is not willing to work with the sponsor during the conduct of a clinical trial? Absolutely not. In this clinical trial, to prevent a disruption in enrollment, FDA approved the addition of an administrative cohort and an alternative perfusion solution after the Sponsor provided data demonstrating its chemical equivalence.

So what are the next steps for the evaluation of this PMA? Unlike a 510(k) where one device is looking to claim substantial equivalence to another legally marketed device, in the case of a PMA, the data of a pivotal clinical trial must stand on its own merit.

And I would like to take this moment to thank the patients that came in and shared their stories, okay? It truly matters, and I truly appreciate you coming in today to share that.

Now, from a regulatory perspective, it's very complicated because what I'm asked to do is to focus on how this device performed according to the study protocol. And it's easy for us to hypothesize about potential benefits that could come from a device like this, including extended lung utility, extended perfusion time. Unfortunately, we're restricted to evaluating the data that's within the study protocol.

So, with that said, we're evaluating the data provided in this PMA submission in its totality, and that means an evaluation of the data collected within the United States and outside the United States and all patients enrolled in the study. While FDA can and does review subgroup analysis, it's important to consider the totality of the evidence, including the data from all participants enrolled in the clinical trial. We believe that selected analysis

of subpopulations may be appropriate for certain marketing and labeling claims, but complete exclusion of a certain group of patients for data analysis is not appropriate for the evaluation of a PMA.

In addition to our analysis of the data, we will be taking into consideration the recommendations of this outside expert Panel to help us with our final evaluation and our decision on this PMA.

So, with that said, with the information that has been presented today and the discussions that have taken place, FDA will be asking the Panel's recommendation on if they feel that with all of the changes that have taken place during the course of this study and the information that's contained in this PMA, does it constitute valid scientific evidence that demonstrates a reasonable assurance of safety and effectiveness of this device for its proposed indication for use?

So, once again, I would like to thank TransMedics, and I would like to thank the members of the Panel for their time and participation today. So thank you very much.

DR. SCHWAITZBERG: Thank you, Dr. Fisher.

I'd now like to take the opportunity to take comments from our nonvoting members, which will be Mr. Frankel, our Consumer Representative; Mr. Thuramalla, our Industry Representative; and Ms. Barnes, our Patient Representative, to see if they have any further comments.

Mr. Frankel, if you'd start.

MR. FRANKEL: First, I want to thank the Sponsor for the extraordinarily important work on this innovative healthcare technology. Without people like the Sponsor focused on innovation, progress in medical devices would obviously not happen. Also, thank you to the FDA for their thorough presentation today, and of course, thank you to the patients for coming.

Focusing on whether there are any patients who will, perhaps, not survive or in any way fare worse due to OCS, and looking at the nature of some of the screen failures, adverse events, increased incidences in surgical harvest complications, and decreased observed short-term survival, I can't confidently know that there won't be specific patients who may fare worse with OCS rather than standard of care, perhaps due in part to extra complexities with the technology. The issues which arose due to the changes in the trial perhaps increased that uncertainty.

Having said that, there's certainly an extraordinary glaring unmet need that needs to be filled, which was powerfully emphasized by the patients who testified today. But these issues were not addressed by the data today but hopefully will be seen with the upcoming trial results.

In conclusion, I strongly support all and any innovation and any options, new options for patients, but if there's any possibility of introducing new risks to a patient versus the standard of care with OCS, I would only be able to support such approval if the patient will be empowered to make that informed choice, which in the context of this device would seem to be difficult versus -- and as opposed to patients without access to standard of care, which I think that such new technology obviously should be made available for, if possible. I hope in the future that this technology will be shown to offer superiority to the standard of care, or at least definitive, clear non-inferiority without new introduced risks for all patients. Thank you.

DR. SCHWAITZBERG: Mr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla. I'd like to take this opportunity to thank the Sponsor for their hard work and dedication spanning nearly 2 decades and for the excellent presentation they gave today. I'd like to also take this opportunity to thank FDA for their very detailed presentation and answering all the Panel member questions. I'd like

to also take this opportunity to thank all the patient representatives and the patients themselves who took the time to come to this Panel and share their experiences. It was very valuable feedback for me. Lastly, but most importantly, I'd like to also thank all the Panel members for such a detailed and thorough discussion on this very innovative product. Thank you.

DR. SCHWAITZBERG: Ms. Barnes.

MS. BARNES: I'd like to thank the FDA for holding this meeting, and I'd like to thank the company for all of your work over these years and the patients who are here and the patients who are not here, either physically or who, you know, didn't survive the process of the disease that they suffered from and maybe from transplant as well.

It is a tough challenge that we're faced with, but I think the one thing we need desperately in pulmonary is advances in technology, advances in innovations. It truly needs to be a shaken-up industry, and I think we can borrow from our friends who are here that have worked at other disease areas and other organ areas, because there's progress in other areas that I think we will all benefit from.

As a family member of multiple patients with deadly lung disease -- and I'm at 50/50 risk myself of a deadly lung disease with no therapy. Pulmonary fibrosis was mentioned earlier; my child is at risk. I believe that the future is now. We cannot have another 30 years with no progress. We have to have technology now. I'm not suggesting that this is the technology, but I think this is a technology, this is something that could help lead the way for more innovative, exciting, life-changing, lifesaving opportunities. Thank you.

DR. SCHWAITZBERG: Thank you, Ms. Barnes.

We're now ready to vote on the Panel's recommendations to the FDA for the TransMedics Organ Care System, OCS Lung System. The Panel is expected to respond to three voting questions relating to safety, effectiveness, and risk versus benefit. Ms. Aden

Asefa will now read two definitions to assist in the voting process, and she will also read the proposed indications for use statement for this device.

MS. ASEFA: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket approval applications (PMAs) that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety and effectiveness are as follows:

Safety as defined in 21 C.F.R. Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness as defined in 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

The Sponsor has proposed the following indications for use: The TransMedics Organ Care System (OCS) Lung System -- intended to preserve donor lungs in a near physiological, ventilated, and perfused state for transplantation.

Panel members, please use the buttons on your microphone to place your vote of yes, no, or abstain to the following three voting questions.

Voting Question No. 1: Is there reasonable assurance that the TransMedics Organ Care System Lung System is safe for patients who meet the criteria specified in the proposed indication?

Please vote now, yes, no, or abstain.

(Panel vote.)

Voting Question 2 reads as follows: Is there reasonable assurance that the TransMedics Organ Care System Lung System is effective for use in patients who meet the criteria specified in the proposed indication?

Please vote now, yes, no, or abstain.

(Panel vote.)

The third and final voting question reads as follows: Do the benefits of TransMedics Organ Care System (OCS) Lung System outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

Please vote now, yes, no, or abstain.

(Panel vote.)

The votes have been captured, and I will now read the votes into the record. On Question No. 1, the Panel voted 11 yes and 2 for no that the data shows reasonable assurance that the TransMedics Organ Care System is safe for use in patients who meet the criteria specified in the proposed indications.

On Question 2, the Panel voted 8 for yes and 5 for no that there is reasonable assurance that the TransMedics Organ Care Lung System is effective for use in patients who meet the criteria specified in the proposed indications.

On Question 3, the Panel voted 9 for yes and 4 for no that the benefits of the TransMedics Organ Care System Lung System outweigh the risks for use in patients who meet the criteria specified in the proposed indications.

The three voting questions are now complete.

DR. SCHWAITZBERG: Dr. Fisher, as a procedural question, do you want the individual votes read now or as we go around the room?

DR. FISHER: Go around the room.

DR. SCHWAITZBERG: All right. I will now ask the Panel members to discuss their votes on each of the three questions. Why don't we do it by question to keep it straight? We'll go by Question 1. If you answered no to any question, please state whether changes to labeling, further restrictions on use, or other controls would make a difference in your answer. State your name and how you voted on Question 1.

Dr. Moon.

DR. MOON: Marc Moon.

I voted yes. I don't think there's any safety concern issues, no negatives to the use of it versus our standard of care.

DR. SCHWAITZBERG: Dr. Meyer.

DR. MEYER: On safety, I voted yes. I did have some comments about the use from a surgical standpoint and how this may need to be added to any kind of an IFU.

DR. SCHWAITZBERG: Dr. Nathan.

DR. NATHAN: I voted yes, I think it is safe. We have to remember that lung transplantation itself is not a safe procedure, and in the context of lung transplantation, I believe it's safe. There's nothing there that I saw that made it appear unsafe.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: I voted no. There is a great rationale for such a technology; the comparator is archaic. The Sponsor and investigators have worked hard to move the field of transplant forward and prove the outcomes in the system, and I do commend them for that, and I wish them success. The many typical problems they noted and agreed with are

understood. They did claim the device was positive; they acknowledge these methodology and data concerns. However, I do not feel that the study met the required endpoints, and so I must disagree with their conclusions, and I will give further comments with the other two questions.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: Jeff Riley.

I voted yes. I believe the positives outweigh the flaws in the protocol.

DR. YUH: I voted yes. I don't think it's an intrinsically unsafe device. The adverse events that were reported I'm not convinced are related to the design of the device, so that's the reason I voted yes.

DR. SCHWAITZBERG: Dr. Afifi.

DR. AFIFI: I voted yes. I had no problem with the safety data.

DR. SCHWAITZBERG: Dr. Hammon.

DR. HAMMON: I voted yes because I believe that the device is desperately needed and that the safety data did not convince me that it was unsafe.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: I voted yes, that I felt that it was safe.

DR. SCHWAITZBERG: Dr. Krupnick.

DR. KRUPNICK: I voted yes. I think the device is as safe as any other technology we use in lung transplantation today.

DR. SCHWAITZBERG: Mr. Stammers.

MR. STAMMERS: I voted yes, and the only thing I'd like to emphasize is I believe that this is still an extracorporeal device, and it just needs to be handled by individuals who are well versed with all the challenges associated there within.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: I voted yes. I had no safety concerns.

DR. SCHWAITZBERG: Dr. Connor.

DR. CONNOR: I voted no. I thought if you showed someone the two Kaplan-Meier curves without a legend and said which one do you want, no one would've said the OCS device, and fewer people would've said I don't care, flip a coin than would have actually said I would rather have an Igloo cooler with ice.

DR. SCHWAITZBERG: Thank you for your comments on Question 1. Why don't we go in reverse on Question 2?

Dr. Connor.

DR. CONNOR: I voted no again, given -- the benefits seem largely hypothetical. I believe they're real, but there isn't data to substantiate them at this point, and I think they're good intentions, and I think it's a great device, and I hope those intentions pan out. But the risks seem very real, that the mITT population, which I think we agreed was the appropriate one, and even it included three times as many exclusions as the standard of care group. Using that with the endpoint that was more clinically relevant of just death or PGD3 at 72, which is clearly more clinically relevant than early ones, it's not just non-inferior, it's actually higher; it is statistically significantly higher within 30 days. So, given that, I could not vote that it offered a clinical benefit.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: Well, looking at Questions 2 and 3, Question 2 seems to me to be very narrowly about did they hit their modified intention to treat target, and the answer to that was no.

DR. SCHWAITZBERG: Mr. Stammers.

MR. STAMMERS: I voted yes, and I think hearing all of the testimony from the Sponsor, I believe they're genuinely concerned with their change in protocol and the FDA

has so eloquently pointed out, but I do believe the down-road benefits are going to outweigh the risk associated with that unfortunate methodological error that they had.

DR. KRUPNICK: I voted yes. I had no issues.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: I voted yes under the very narrow expectation that the stated use was the ability to transport with no statements about PGD or BOS, which I believe was very similar to the safety question, which is why I said yes.

DR. SCHWAITZBERG: Dr. Hammon.

DR. HAMMON: I voted yes. I had no issues.

DR. SCHWAITZBERG: Just a short comment before we go on. I think the Sponsor should really take heed to their comments about never doing a trial like this again because this is actually a pretty near thing while I watched the votes materialize. I think you're hearing some comments about the change in methodology to per protocol could have turned out differently, very differently, and so I wouldn't necessarily take this as a massive endorsement.

If we could continue.

DR. AFIFI: I followed Dr. Fisher's admonition to look at the totality of the data, and based on that, I was not persuaded that there was evidence of equivalence or non-inferiority.

DR. SCHWAITZBERG: Dr. Yuh.

DR. YUH: So I voted no. You know, as I stated before, the change in definition did give me pause, and under the modified intention-to-treat framework, it didn't pass muster either, so looking at the data and answering the question directly, I had to vote no.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: I voted yes, but it was a 60% yes for all the reasons stated by the "no"

persons. The indication for use will not be followed. We'll take this device, like we take every new device, and use it off label as soon as we get it in our hands.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: Are we doing Question 2, or 2 and 3? Just 2?

DR. SCHWAITZBERG: We're just doing 2, one at a time.

DR. YUSEN: Okay. I'd first like to correct a statement I made last time. I do understand that the non-inferiority threshold was met for safety, but I still vote the same way, and that's again based on a methodology in reporting concerns.

Regarding efficacy, I have the same opinion. I voted no again, based on the trial methodology concerns and based on the evidence that was shown.

DR. SCHWAITZBERG: Dr. Nathan.

DR. NATHAN: I voted yes. I think that the device is effective, survival at 1 year, 2 years was exactly the same, so it's effective in getting patients transplanted as safely as standard of care.

DR. SCHWAITZBERG: Dr. Meyer.

DR. MEYER: I voted yes. I think after the initial 30-day drop, the device looks as effective as the cold storage.

DR. SCHWAITZBERG: Dr. Moon.

DR. MOON: I voted yes, summarizing that it's not more effective than the standard of care like they tried to suggest to us, based on leaving some patients out of the analysis that should've been in the analysis. But I would say that it is probably as effective as the standard of care; therefore, it should not become the standard of care but could be considered. And the reason I want it approved is so that it can be used for these other indications where it may actually be more effective, for example, assessing marginal lungs and lung transplant times from cross-clamp. And, also, the label doesn't really say anything,

I don't think, so it could be used for anything.

DR. SCHWAITZBERG: Yeah, I would echo that comment. The labeling is pretty vague.

We'll go around the room for the third question. We'll start with Dr. Afifi, and then when we get to the end, we'll go to Mr. Hammon because that's the only scheme that I haven't used yet today.

DR. AFIFI: Since I voted no on Question 2, it was only logical to also vote no on Question 3. Since the non-inferiority was not shown, I cannot say that the benefit outweighs the risk.

DR. YUH: By the same token, I should have voted no on 3 based on my question [sic] to Answer No. 2, but the upside of this device is so compelling, and although the data didn't convincingly and statistically show me benefit, it didn't -- it couldn't show me otherwise either. And so, in terms of the bottom line to Question No. 3, I just saw the upside so compelling in terms of being able to expand the donor pool, lending more flexibility logistically to procurement, increasing the cross-clamp time, and even the theoretic benefits on BOS, although not shown in the study, that there is clearly precedent for taking that tack, I had to vote yes on Question No. 3.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: I voted yes on Question No. 3 because I voted yes on 1 and 2, logically, following logic. I was comforted by the European experience, and I'm also comforted by the four presentations I've seen by our colleagues showing how they use this device clinically. So I was okay, forgiving the flaws in the protocol.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: I voted no for risk-benefit. I think the risk-benefit for this technology remains unclear. The need for new technologies is important, but it should not drive the

interpretation of the study design and the data, and I do hope the Sponsor will continue to work on testing and refining this technology because of its great potential.

DR. SCHWAITZBERG: Dr. Nathan.

DR. NATHAN: I voted yes for benefits not only based on the data but also on some of the intangibles we all heard about and especially during the public part of this forum today.

DR. SCHWAITZBERG: Dr. Meyer.

DR. MEYER: I voted yes based on the benefits, and the only caveat is hopefully the practitioners will use this for the indication that the study was intended for and, down the line with further studies, expanding the indications.

DR. SCHWAITZBERG: Dr. Moon.

DR. MOON: I think the risk is low and the benefit has potential, so potential over low wins risk over -- or benefit over risk.

DR. SCHWAITZBERG: Thank you.

Dr. Hammon.

DR. HAMMON: I voted yes for benefit, and I hope the Sponsors will continue to improve the performance and the outcomes.

DR. SCHWAITZBERG: Dr. van Berkel.

DR. VAN BERKEL: So I voted no on risks or benefits. I think I agree with everyone else that there is incredible potential here, and I think that we're all eagerly anticipating, as I stated earlier, the EXTEND trial. I do not think that there is anything here that demonstrated benefit today. I think that there is, at best, no difference from standard of care, and I think that of course there is risks associated with doing this; it's complicated, and it's expensive. And so while I join everybody else in the hope that this is going to be beneficial in the future, I do not think that what we saw today demonstrates that.

DR. SCHWAITZBERG: Dr. Krupnick.

DR. KRUPNICK: I voted yes. I believe the benefits outweigh the risk.

DR. SCHWAITZBERG: Mr. Stammers.

MR. STAMMERS: Yes, exactly what Dr. Krupnick said.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: I voted yes.

DR. SCHWAITZBERG: Dr. Connor.

DR. CONNOR: I voted no. One of the questions was would a label-change change anything? So I'm happy this technology exists, and I know I've been very critical, and I commend the Sponsor for the development of the technology. One of the comments I would make about the label is that it seems great for those cases where there are remote organs or remote recipients. I think it was Mr. Johnson, and I apologize if I got that wrong, with a large set of lungs, people who are difficult to match, I think it contains great benefit for such patients. And I also understand the ethics here, right? This isn't a finite -- or we have a finite number of lungs. It's not like a product where we can always manufacture more of, that the benefits seem hypothetical and maybe increase the number, but for individual patients, I just did not see where the benefits outweighed the risks.

DR. SCHWAITZBERG: I'd like to thank the Panel for their comments and certainly the Sponsors for their contributions.

Dr. Fisher, do you have any final remarks?

DR. FISHER: I would just like to solicit one last comment, and I've heard some stuff about -- a few comments on labeling, and I was wondering if anybody else had any comments on things that should be included or excluded in the labeling, if we could capture any comments that you might have. One last round.

DR. SCHWAITZBERG: All right, we'll go around. Dr. Moon, comments on labeling?

DR. MOON: Can we see the label again? Is that possible, or is everything shut off? Anyway, I think it just should imply that -- well, I don't even know what to say. But I don't think they should say in there it's better than the standard of care.

DR. SCHWAITZBERG: The Sponsor has proposed the following indications for use: The OCS System is intended to preserve donor lungs in a near physiologic, ventilated, and perfused state for transplantation. That's the proposed indication.

Dr. Meyer, any comments?

DR. MEYER: I would just make sure there's information regarding the qualifications for use by the surgeon.

DR. SCHWAITZBERG: Would you limit it by population?

DR. MEYER: Yeah, I would limit it to the group that was studied, as the proposed potential indications and benefits have not been --

DR. SCHWAITZBERG: Double-lung transplants.

DR. MEYER: Yes, double.

DR. SCHWAITZBERG: Dr. Nathan.

DR. NATHAN: I would keep it the same. It's simple, it's broad, and I'd leave it in the hands of the clinicians to figure out, and market forces will dictate, how it's used and clinical experience will also dictate how it's used.

DR. SCHWAITZBERG: Dr. Yusen.

DR. YUSEN: I would vote in favor of being conservative and using it in the way it was studied. You know, this was not a study focusing on marginal donors, and it was not a study of single-lung transplant; it excluded DCD, a lot of other caveats with lung trimming, lobectomy. I think this ought to be studied further formally if it's going to be used in other populations and other degrees of disease severity.

DR. SCHWAITZBERG: Mr. Riley.

MR. RILEY: I'm for open and broad with Dr. Nathan, but I was surprised there wasn't a time limit in the indication. Most of the devices, the extracorporeal devices we have today, are approved for 6 hours of use just on the extracorporeal components alone, so I was a little bit shocked that there wasn't a time limit or a warning on that. But other than that -- and when I was being flip about using it off label, I was talking about having lungs on it for a week or 2 weeks, waiting for pneumonia to repair itself, but I don't think that's so far-fetched.

DR. SCHWAITZBERG: Dr. Yuh.

DR. YUH: I think the broad indications are appropriate at this stage. We just don't have enough data to really parse it down to specific indications or contraindications or specific populations, at least at this stage.

DR. SCHWAITZBERG: I think the labeling for the indications of the populations studied is really the only place you can go at the moment.

Dr. Hammond, Hammon.

DR. HAMMON: I agree with the labeling that Dr. Schwaitzberg read.

DR. VAN BERKEL: So I think my concern is that the broadness of the labeling, and I freely admit that I don't know how to answer this problem, but the broadness of the labeling, you know that as soon as this gets out in the wild and people say like, oh, they're going to treat it like a kidney, they're going to say, hey, we got it on a rig, it's fine, we'll do it in the morning; we don't have to do it at midnight, we don't have to do it at ten o'clock, we'll do it tomorrow. Or if, you know, it's a weekend, maybe we're going to wait until Monday or we're going to do something -- someone out there is going to do something stupid like that, and we don't -- we do not have the data. That is our hope, like our dream is that we're going to be able to do that with these lungs. We do not have the data to support that. And that was my risk-benefit argument here.

I think that as soon as we put it out there with a broad label like this that basically says, hey, it's there to like, you know, to keep it physiologic, someone is going to stretch the bounds of that past what we know is useful. And there may be some -- maybe that'll be great, and maybe we're going to find that there's no problem there, but we might actually find that there's a problem there. And I think that that should be done in the context of a trial rather than just people trying stuff.

DR. SCHWAITZBERG: Dr. Krupnick.

DR. KRUPNICK: Yeah, I'm going to kind of agree with Dr. van Berkel. I can see, although I voted yes because, you know, I think they proved their study, but you know, I can see the concerns. This kind of reminds me of a story, you know, about 10 years ago I bought my kid a Superman outfit, and there was really a sticker on it that really said this suit does not enable one to fly.

(Laughter.)

DR. KRUPNICK: And, you know, it's something similar. You can't take a lung with pneumonia, can't take, you know, a lung with terrible COPD and put it on this machine. So I guess it does have to be labeled, but a lot of that will depend on, you know, the surgeon preference. But I agree with you that, you know, there is the danger of people taking it overboard.

DR. SCHWAITZBERG: Mr. Stammers.

MR. STAMMERS: Yes, I agree that the labeling should be more conservative and directly, of course, related to the trial itself. It's very broad right now, and I like what Jeff had said because although the componentry within the disposable set was not defined or at least in literature that I received, it looked like the device that was in that was a device that either the FDA had cleared for use at 6 hours or cleared for use for ECMO; I couldn't determine directly. So there is a time limitation potential on the blood gas exchange device

that is in the circuit, I believe. Again, I didn't see the nomenclature, so it could be something else. But definitely, as Jeff had said, timing may be an issue.

DR. SCHWAITZBERG: Dr. O'Connor.

DR. O'CONNOR: So if we're going to base our labeling exclusively on the data we have before us, it seems that we could say that the device should be indicated for use in people in whom a long ischemic time would be of benefit to the patient, the recipient, and that would largely be related to longer transport distances or times.

DR. SCHWAITZBERG: Thank you.

DR. O'CONNOR: Because there's clearly evidence that the lungs tolerate that in this study. There's nothing about difficulty cross-matching, there's nothing about size matching, there's nothing about the lung evaluation. It's really all about these lungs will tolerate a longer time out of the body.

DR. SCHWAITZBERG: Dr. Connor.

DR. CONNOR: Yeah, I certainly appreciate that FDA cannot legislate the practice of medicine and certainly cannot control the behavior of surgeons. That said, I think Dr. Berkel's comment -- right, Dr. Berkel's suggestion is -- or concern is very fair, and I think a label that is appropriately cautious would be appropriate.

DR. SCHWAITZBERG: Dr. Fisher, does that answer your question?

DR. FISHER: Yes. And I would like to thank all the Panel for that second go-around. Thank you very much.

DR. SCHWAITZBERG: So I would like to thank the Panel and the FDA for the privilege of chairing this meeting, and without any further ado, although we are 1 minute over, this meeting is closed.

(Whereupon, at 6:02 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GASTROENTEROLOGY AND UROLOGY DEVICES PANEL

May 17, 2017

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TOM BOWMAN

Official Reporter